ABSTRACT

THE OHIO STATE UNIVERSITY SCHOOL OF ALLIED MEDICAL PROFESSIONS

The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion

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OBJECTIVE: The purposes of this study were to determine if relationships existed between cracking pressures of -7, -11, -15, and -19 cm H_2O vs. cardiopulmonary physiologic parameters and Borg scale scores for healthy adults and to determine the maximum cracking pressure which does not produce a Borg score greater than 6. DESIGN: The study was designed as single blinded, randomized, and quasi-experimental with repeated measurements. Subjects served as their own controls. SETTING: Laboratory. SUBJECTS: 21 healthy, normotensive, normovolemic volunteers. METHODS: Subjects were continuously observed and monitored using bioimpedance for non-invasive cardiac output and heart rate, respiratory frequency and pulse oximetry. Subjects breathed through an Impedance Threshold Device (ITD) alternating between two-minute intervals of zero resistance and resistances of -7, -11, -15, and -19 cm H_2O pressure. For randomization, subjects selected pre-set ITDs from a set of 4. During each level of resistance, maximum changes from baseline of cardiac output (CO), heart rate (HR), blood pressure (BP), respiratory rate (RR) and arterial oxygen saturation (SpO_2) were recorded and subjects indicated their subjective feeling of exertion based on a Borg scale score from 1 to 10. RESULTS: There was a statistically significant strong negative correlation between cracking pressures and Borg scale scores ($r = -0.814$, $p < 0.01$). The percentage of subjects indicating a score of 6 or greater increased as the cracking pressures became more negative (0% - 43%). There were no statistically significant correlations between the cracking pressures and any of the physiological variables measured. An ANOVA analysis indicated that there were no statistically significant differences between the means of any physiological variables while subjects were breathing on the 5 cracking pressures. CONCLUSIONS: While the ITD can make normovolemic, normotensive, spontaneously breathing individuals feel like they are exerting more effort as the magnitude of its cracking pressure becomes more negative, there is no evidence to support that it causes any physiological changes within a 2 minute time period.

Advisor's Signature

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The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion

An Undergraduate Honors Thesis

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Table of Contents

Chapter I

Introduction

Problem Statement

Within the last five years, several studies have been conducted assessing the possibility of using induced negative intra-thoracic pressure to increase cardiac output (CO). Subatmospheric intrathoracic pressure, which is referred to as "negative pressure," naturally occurs within a person's thoracic cavity when they take an inspiration.[1] Almost everyone must create a substantial amount of negative pressure within their thoracic cavity to allow airflow into their lungs. However, this negative intra-thoracic pressure can be increased to a greater intensity by adding some resistance to a person's inspiration.[2] It is believed that with this technique of inducing an increase in negative pressure within the thoracic cavity, blood return to the heart will increase.[3] Because the heart receives more blood, the heart contracts more forcefully, due to the Frank Starling Mechanism, which increases its cardiac output.[1]

It has been suggested that it may be possible to use negative intrathoracic pressure to treat people who are in a state of hypovolemia or hemorrhagic shock.[3, 4] People, who are in these conditions, typically experience poor blood circulation within a short period of time. By temporarily increasing a person's CO with the usage of induced negative intrathoracic pressure, it is believed that the survival times of people in these states will be increased.[4] Researchers have suggested that negative intrathoracic pressure should be induced within these people with the aid of an impedance threshold device (ITD).[3, 4]

The ITD is a tool designed to temporarily increase the CO and stroke volume (SV) of someone's heart by impeding their breathing for a short period of time each time they inhale through the device.[2-4] Initially, when its user inhales through the device, an air seal within the ITD will prevent air from entering into their lungs.[2-4] However, since the user's lungs are continually expanding, the negative pressure decreases within their lungs. Eventually, the decreasing negative pressure within the user's lungs will become low enough to cause the air seal within the ITD to crack open, allowing air to flow into their lungs.[2-4] Each ITD is set to allow air to flow in at a specific "cracking pressure," which is the term assigned to describe the amount of negative pressure one's lungs must create before the ITD will "crack open" its air seal.[2-4] Typically a person will only need to use a fraction of their generated negative pressure to overcome this cracking pressure.

Despite the amount of research being done on the possible benefits of the ITD, there has been no clear standard as to what cracking pressures the ITD needs to be in order to enable its effects on CO and SV. As of now, we only know that an ITD should be set within a certain range of cracking pressures. For example, an article by Lurie suggests that the lowest possible cracking pressure that induces its hemodynamic effects should be used due to the possibility of operator error.[2] However, in his conclusion he does not leave a decisive value as to what the cracking pressure should be and instead just suggests a pressure range of -5 to -15 cm H_2O.[2] Several other studies have been using an ITD with a cracking pressure of -7 cm H_2O on people, but it had also been determined that people were willing to tolerate pressures of up to -20 cm H_2O.[2, 3, 4] Currently, there are several different versions of the ITD being sold for different situations that occur

within the hospital, with cracking pressures of -7, -10, and -16 cm H_2O, but no baseline has been set as to what cracking pressure will allow a person with healthy, normal lungs to increase their CO and not experience a sensation of having to work hard to breathe (J. Flom, personal communication, April 13, 2007).

Chapter II

Review of the Literature

Literature was obtained from the internet service Pubmed and the on-line research database at The Ohio State University using the keywords, "impedance threshold device," "negative intra-thoracic pressure," "cardiac output," and "modified Borg scale for perceived exertion." The results of the searches were used to identify the feasibility of using an ITD to enhance CO, the set cracking pressures of the ITD used in previous experiments, and a scale that could be used to identify the amount of effort someone feels they are exerting when using an ITD. The results of the searches provided background information on the mechanism of the ITD itself, the physiological effects the ITD causes when someone is breathing on it, and the methods researchers used to measure the effects of the ITD.

History of the ITD

In 2003, Lurie et al assessed a prototypic ITD, which was called an "inspiratory threshold valve" at the time, in the project titled, "Evaluation of a Prototypic Inspiratory Impedance Threshold Valve Designed to Enhance the Efficiency of Cardiopulmonary Resuscitation."[2] The study focused on the testing of the durability and efficacy of the ITD. From their study, they found that the ITD was durable enough to use in a clinical setting in accordance to the "American Society for Testing and Materials (ASTM) and International Standards Organizations (ISO) guidelines."[2] They also found that the ITD did increase the magnitude of subatmospheric intrathoracic pressures within its user's

chest cavities while they were undergoing active compression/decompression CPR.[2] After measuring the intrathoracic pressures generated by 6 anesthetized pigs, using an ITD with a cracking pressure set at -10 cm H_2O, they recorded a -6 to -8 cm H_2O decrease of intrathoracic pressure within those pigs.[2] Therefore, it was assumed by Lurie that the ITD does decrease negative intrathoracic pressure and will not break easily when used in a clinical setting.

In addition to proving that the ITD did decrease negative intrathoracic pressure, it was emphasized by Lurie that the lowest possible cracking pressure to achieve its hemodynamic benefit should be used. This point was emphasized because there was a possibility that a person, who was revived from CPR and did not have their spontaneous breathing recognized by their rescuer, may be forced to breathe through an ITD for a period of time.[2] Therefore, the least amount of cracking pressure should be used so that a user of the device can spontaneously breathe without having to feel like they are struggling to breathe.[2] The study determined that the cracking pressure should be set at -10 cm H_2O, because that allowed the most airflow through the ITD.[2] However, this pressure was selected only on the basis of how much inspiratory airflow could flow through the ITD and not on how comfortable people felt when using the ITD.[2] Also, Lurie noted that previous clinical trials, which studied the effects of the ITD on CPR, had the cracking pressures of the ITD being used set at -35 cm H_2O and -24 cm H_2O, which were at least two to three times higher in magnitude than the cracking pressure recommended by this study.[2] This made it seem plausible that an ITD set at these pressures would not harm the subjects using the device. Unfortunately, further research

on a human subject's tolerance to the higher pressures was not assessed because of Lurie's emphasis on trying to keep the ITD's cracking pressure as low as possible. In Lurie's conclusion, it was suggested that an ITD with a cracking pressure of -5 to -15 cm H_2O would be adequate enough to increase circulation throughout the body.[2]

In 2004, Lurie et al focused on observing the physiologic effects of the ITD that occurred when it was being used by spontaneously breathing subjects. In the study, "Treatment of hypotension in pigs with an inspiratory impedance threshold device: A feasibility study," thirty-nine female pigs were sedated, left to spontaneously breathe on their own, divided, and assigned to one of four groups.[3] Each group had one of four experiments done on them. The experiments included studies on the effect of the ITD on systolic blood pressure (SBP) at the cracking pressures of 0, -5, -10, -15, and -20 cm H_2O, the usage of a -12 cm H_2O ITD on subjects that were bled to SBPs of 50 to 55 mm Hg (hypovolemic subjects), the effects of the ITD on a cardiac output value calculated from mixed venous and arterial blood gas values obtained from hypovolemic subjects, and the effects of the ITD on the cardiac output value obtained from the usage of the thermodilution method on hypovolemic subjects.[3] The experiment evaluating the various cracking pressures was done first so that they could determine which cracking pressure they should use for the other three experiments.[3] They measured their subject's blood pressures (BP) continuously while the subject was breathing on ITD's of different cracking pressure magnitudes according to the timeline as show in Table 1.[3] The researchers then determined that they should select a cracking pressure of -12 cm H_2O based on their observations of how difficult it was for the sedated pigs to breathe on

Table 1. The Experiment Timeline for Measuring Different Cracking Pressures

2 min	2 min	2 min	2 min	2 min	2 min	2 min	2 min	2 min
0 cm H_2O	-5 cm H_2O	-10 cm H_2O	-15 cm H_2O	-20 cm H_2O	-15 cm H_2O	-10 cm H_2O	-5 cm H_2O	0 cm H_2O

an ITD set at a cracking pressure of -20 cm H_2O.[3] From the four studies, it was concluded that increasing the magnitude of the cracking pressure set on the ITD did significantly increase the SBP of their subjects, the ITD did increase a hypovolemic subject's BP ($p<0.01$), and the ITD did increase the cardiac output of the hypovolemic subjects by 25% ($p<0.01$).[3] A two minute interval was an adequate amount of time for the hemodynamic effects of the ITD to occur.[3] Also, when comparing a group of pigs breathing on a -12 cm H_2O ITD to a group of pigs who were breathing on a 0 cm H_2O ITD, the SBPs were indistinguishable between the two groups after the group, using the -12 cm H_2O ITD, was taken off their ITD.[3] Therefore, it is assumed that it only took a short amount of time for subjects to experience the effects of the ITD and recover from the effects of the ITD.

In addition to these results though, there were a couple of negative issues with this study by Lurie. They found that the PaO_2 levels within the hypovolemic pigs that were using an ITD decreased, on average, to 87 mm Hg from a baseline of 94 mm Hg.[3] However, Lurie indicated that the arterial oxygen saturation levels never decreased below 88% within their subjects and that their subject's PaO_2 levels did closely return their initial baseline values, which was 93 mm Hg, after they were taken off the ITD.[3] Also,

while measuring the hemodynamic effects of the various cracking pressures, the study only focused on recording the BP of the subjects and not the CO of the subjects.[3]

In 2004, Covertino et al began to study the physiologic effects of the ITD on human subjects. The study, "Hemodynamics associated with breathing through an inspiratory impedance threshold device in human volunteers," focused on the hemodynamic and respiratory responses of subjects who were spontaneously breathing through an ITD.[4] Twenty subjects were asked to breathe through an ITD, with a cracking pressure set at -6 cm H_2O, or a sham ITD, with a cracking pressure set at 0 cm H_2O, while having their heart rate (HR), stroke volume (SV), arterial BP, and tidal volumes measured.[4]

Multiple tools were used to measure the subject's aforementioned physiological variables. Subjects breathed through both devices for five minutes at different times with an electrocardiogram (ECG), automated sphygmomanometer, and a thoracic electrical bioimpedance device attached to them.[4] The ECG measured the subject's HR, the automated sphygmomanometer measured the subject's BP, and the thoracic electrical bioimpedance device measured the subject's SV.[4] The average SVs of ten cardiac cycles was determined to be the SV the subject had while breathing on the ITD.[4] A CO was calculated by multiplying the average SV and the HR the subject had while they were breathing on the ITD.[4] A turbine transducer, which was attached to the subject's ITD, was used to measure the subject's minute ventilation.[4] A MKS pressure transducer was attached between the ITD and subject's facemask to measure their respiratory rate (RR).[4]

Both the measured minute ventilations and RRs were used to calculate the tidal volumes of the subject.[4]

Convertino's study revealed that when subjects were breathing through the ITD, they had "higher SV (124 mL vs. 137 mL; p = 0.013), HR (63 beats/min vs. 68 beats/min; p = 0.049), CO (7.69 L/min vs. 9.34 L/min; p = 0.001), and SBP (115 mm Hg vs. 122 mm Hg; p = 0.005)" than when they were breathing through the sham ITD.[4] All of these effects occurred "without affecting the inspired minute ventilation (6.2 vs. 6.5 L/min; p = 0.609). The study indicated that the ITD did have an influence on CO and could be used without altering the breathing pattern of their human subjects. Also, since all the cracking pressures used in other studies had used cracking pressures with a magnitude greater than -6 cm H_2O and that the study's human subjects experienced approximately a 1 L/min increase in CO when using the ITD, it was assumed that there should be at least a 1 L/min increase in CO for an ITD to be considered effective.[2-6] However, all of these values only correspond to an ITD with a cracking pressure set at -6 cm H_2O. There was no range of cracking pressures tested. Also there was no evaluation on how the subjects felt while they were breathing on the ITD.

In 2007, Cooke et al studied the effects of the ITD on the autonomic cardiovascular system and cerebrovascular system in healthy subjects in the study titled, "Human Autonomic and Cerebrovascular Responses to Inspiratory Impedance."[5] The purpose of the study was to determine if the "autonomic cardiovascular system or dynamic cerebral autoregulation," which can increase CO and HR during times of stress, was playing a role in influencing the cardiac effects of the ITD.[5] The study had 8 subjects

breathe through an ITD, with a cracking pressure set at -6 cm H_2O, or a sham ITD, with a set cracking pressure of 0 cm H_2O, while they had their arterial BP, cerebral blood flow velocity (CBFV), muscle sympathetic nerve activity, end tidal CO_2, and inspiratory pressure measured.[5] Subjects randomly breathed through both devices at different times.[5] The study revealed that the ITD increased "mean arterial pressure (MAP) by 5 mm Hg, HR by 2 bpm, and mean CBFV by 10% ($p < 0.05$) without having any effect on muscle sympathetic nerve activity or estimates of vagal-cardiac control ($p > 0.05$)."[5] The cardiac effects of the ITD were shown to be independent of the sympathetic system and vagal withdrawl.[5]

In 2007, another study, conducted by Idris et al, focused on how much work of breathing was required for someone to breathe through an ITD.[6] Twenty-nine people were required to spontaneously breathe through an ITD, with a cracking pressure set at -7 cm H_2O, or a sham ITD, with a cracking pressure of 0 cm H_2O, while having their HR, RR, tidal volume, exhaled minute ventilation, inspiratory pressure, and inspiratory time measured.[6] Subjects were found to have no significant differences in the HR, RR, tidal volume, or minute ventilation while breathing on the ITD or the sham.[6] However, there was a higher "power of breathing," the work of breathing done in a minute, requirement for subjects to breathe through the ITD than the sham.[6] It required 8.18 J/min to breathe through the ITD and only 0.92 J/min to breathe through the sham.[6] Idris suggested that, for healthy people, this power of breathing requirement was considered to be a tolerable amount of work.[6] Since healthy people usually required a power of breathing of 80 J/min to do just moderate exercise, it was determined that healthy subjects should be able to

require the work of breathing required by the ITD set at a cracking pressure of -7 cm H_2O.[6]

Another study in 2007 done by Rickards et al evaluated the effects of the ITD on CBFV.[7] Eight subjects were exposed to lower body negative pressure (LBNP) to simulate reduced central blood volume.[7] It was believed by the researchers that maintaining a person's CBFV would increase their tolerance to reduced central blood volume which would delay their onset of presyncopal symptoms.[7] During their exposure, the subjects had their HR, SV, SBP, diastolic blood pressure (DBP), CBFV of their right middle cerebral artery, end tidal CO_2, and RR measured while they were breathing on a sham ITD or an ITD set at -7 cm H_2O.[7] Their CO was calculated multiplying the subject's SV with their HR.[7] The subjects breathed on both the sham ITD and the ITD set at -7 cm H2O and had their results compared to their LBNP baseline values with a student's t-test and a two-way analysis of variance for repeated measures.[7] From this study, it was found that the ITD did delay the onset of presyncopal symptoms (From 2,104 ± 106s to 2,259 ± 138 s, P = 0.006) and increased the total oscillations of CBFV (active 45.6 ± 10.2 cm/s^2 vs. 22.1 ± 5.4 cm/s^2, P = 0.004).[7] However, the ITD did not maintain CBFV (sham, 44 ± 4 cm/s vs. active, 47 ± 4 cm/s; P = 0.587).[7] Therefore, it was concluded that the benefit of using the ITD did not result from any ability to maintain CBFV.[7] The ITD worked on other physiological variables, possibly increasing the oscillations of CBFV, to delay its user's presyncopal symptoms.[7]

Validation in Using Thoracic Electrical Bioimpedance to Measure Cardiac Output

In 2002, Sageman et al compared the measurement of CO between the thoracoelectric bioimpedance device (TEB) and thermodilution technique in the study titled, "Equivalence of Bioimpedance and Thermodilution in Measuring Cardiac Index After Cardiac Surgery."[8] Twenty post-cardiopulmonary bypass subjects were selected to have their cardiac output continuously measured with a TEB and the thermodilution technique simultaneously.[8] The TEB "provided a near-continuous measure of CO and cardiac index by measuring SV of each heartbeat and averaging that over a number (chosen by the user) of cardiac cycles."[8] It was a non-invasive device that could calculate the CO of the subject by measuring the SV it detected through its chest and neck electrodes attached to the subject.[8] The thermodilution technique monitored CO invasively. It was already known that the thermodilution technique was merely an estimate of cardiac function, but the gold standard Fick measurement of cardiac index was very difficult to perform in an ICU.[8] Therefore, Sageman decided to compare the TEB device to the thermodilution technique to make a clinically realistic comparison.[8] The cardiac outputs of the subjects acquired by the two devices were evaluated using linear regression, Lin's concordance correlation coefficient, bias, and precision measures for data.[8] The difference between the cardiac outputs, measured by the two devices, for each subject was also calculated.[8]

It was found that the TEB and thermodilution technique did not have much difference between their measurements of cardiac output. There was a linear relationship between the TEB and thermodilution technique, the measurements of the TEB did not

differ clinically from the measurements acquired by the thermodilution technique, and the TEB and thermodilution technique measurements were equivalent for all patients.[8] The COs calculated by the TEB and thermodilution technique were linear in regression and had a Lin's concordance of 0.99.[8] The measurements had a bias of 0.07 L/min/m2 and a precision of 0.4 L/min/m2, which were believed by Sageman, to be within acceptable clinical limits.[8] Therefore, the study concluded that the measurements done by the TEB were equivalent to the thermodilution cardiac index in post operative cardiac surgery patients.[8] It was deemed as an acceptable form of non-invasive monitoring of CO.

Validation in Using the Modified Borg Scale to Evaluate a Subject's Perceived Exertion

In 2007, Grant et al compared the reproducibility of results of the visual analogue scale (VAS), modified Borg scale, and Likert scale (LS) in the study titled, "A Comparison of the Reproducibility and the Sensitivity to Change of Visual Analogue Scales, Borg Scales, and Likert Scales in Normal Subjects During Submaximal Exercise."[9] The study evaluated twenty-three males with the VAS, Borg scale, and LS while they were doing submaximal activities.[9] Submaximal activites were defined as activities that stimulate normal every day life.[9] A subject's submaximal activities protocol was determined based on their VO_2 max, HR, and respiratory exchange ratio that was measured while they underwent a symptom-limited maximal treadmill test.[9] A submaximal activity was an activity that required 60% of the subject's VO_2 max for an initial 2 minute period and then 70% of the subject's VO_2 max for a 6 minute period.[9] Subjects were evaluated once a week for a four week period.[9] During each evaluation,

subjects did four identical submaximal trials and reported their VAS, Borg scale, and LS scores.[9] Two of the submaximal trial results were used to assess the reproducibility, the proportion of total variance reported as a percentage, of the subject's answers.[9] The other two submaximal trial results were used to assess the sensitivity to change the VAS, Borg scale, and LS was able to identify after the subjects took propranolol, which increased a subject's sense of breathlessness and fatigue, or a placebo.[9] Overall, it was found that, out of the three scales evaluated, the VAS yielded the most reproducible results. The VAS was the suggested to be the best to scale to use due to its reproducibility coefficient of 78%.[9] However, the Borg scale was suggested to be the scale that was most sensitive towards detecting general fatigue.[9] Therefore, it could be assumed that the Borg scale is suitable for use towards detecting the amount of work a subject feels they are exerting.

Possible Applications of the ITD on Healthy, Normovolemic, Normotensive People

In 2005, Convertino et al. compiled a review considering the usage of the ITD on people experiencing acute hypovolemia in his review article titled, "Inspiratory Resistance as a Potential Treatment for Orthostatic Intolerance and Hemorrhagic Shock."[10] Convertino suggests that the ITD could provide a suitable way to "reduce postflight orthostatic hypotension in astronauts, and to support brain perfusion in victims of severe traumatic blood loss."[10] The main function of the ITD, which is to improve blood perfusion, may provide a prophylactic effect on conditions where a sudden decrease in blood perfusion is evident. Based on his evaluation of previous studies, which included observations on the ability to use the chest "as an Active Vacuum Pump," "changes of central hemodynamics during resistive breathing," autonomic function of

people while breathing on an ITD, changes of cerebral blood flow perfusion while breathing on an ITD, effects of the ITD on people experiencing orthostatic stress, and effects of inspiratory resistance on people experiencing simulated central blood loss, Convertino came to the general conclusion that the ITD would be able to sustain enough blood perfusion to "restore central blood volume." [10] The results of these other studies showed that the ITD could be used to improve blood perfusion.

The review highlighted several facts. While humans breathe on the ITD, the negative pressure inside the chest "decreases left ventricular and right atrial pressures, consequently increasing left ventricular preload and SV index,"[10] Breathing on the ITD causes the HR, SV, and CO to increase and the total peripheral resistance (TPR) to decrease.[10] The ITD has the ability to reduce muscle sympathetic nerve activity (MSNA), which could make it "an effective countermeasure against syncope and hemorrhagic shock," and it increases mean CBFV.[10] Also, it was demonstrated that humans, who were breathing on the ITD, could sustain or increase blood perfusion while they were experiencing orthostatic stress LBNP.[10] These facts support Convertino's assumption that the ITD could be "used to reduce postflight orthostatic hypotension in astronauts and to support brain perfusion in victims of severe traumatic blood loss."[10] Convertino's review provides enough evidence to suggest that the ITD could be used to manage acute hypotensive conditions.

In 2005, Eiken et al. did further studies on the relationship between motion sickness and blood pressure in his article titled, "Motion Sickness Decreases Arterial Pressure and Therefore Acceleration Tolerance."[11] Eiken observed the effects of motion

sickness (MS) on arterial pressure.[11] Nine healthy men were exposed to an increased G load, G tolerance, until they could no longer tolerate it while having their mean arterial pressure (MAP), HR, electromyographic activity (EMG), the difference in skin temperature between their forearm and tip of their second finger ($\Delta T_{forearm\text{-}fingertip}$), and motion sickness ratings measured.[11] The men were exposed to an increased G load by being centrifuged.[11] The subjects underwent centrifugation two times. They had a motion sickness provocation (MSP) run and a control (CTRL) run.[11] During the MSP run, subjects were exposed to an alternated G load "between 1.4 and 2.5 G at 15-s intervals… [while they were] instructed to turn [their] head to the left and right and to tilt [their] head up and down."[11] Subjects were exposed to conditions that were intended to make them motion sick during the MSP run. During the control run, the G load was increased slowly "by 0.05 G • s^{-1} from 1.4 to 2.5 G and was maintained at this level for 5 min.[11] The G load was then decreased by 0.05 G • s^{-1} to +1.4 G and maintained at this G level for 5 min… [while the subjects were] instructed to forward and keep [their] head still."[11] The subjects were exposed to a "cumulative" amount of G load over time without MSP.[11] While the subjects underwent MSP during centrifugation, their ability to tolerate G load decreased from 5.1 ± 1.0 G (mean ± SD) to 4.6 ± 0.9 G. [11] Also, their MAP decreased by 11 mm Hg and their $\Delta T_{forearm\text{-}fingertip}$, decreased by 4.2 ± 4.1 ˚C.[11] There were no changes in the subjects' ability to tolerate G load, MAP, or $\Delta T_{forearm\text{-}fingertip}$. Although HR was not significantly reduced, the decrease in MAP suggests that there likely is a relationship between cardiovascular function and MS.[11] Eiken concludes that the reduction of arterial pressure, which appears to have a relationship with MS, causes an individual to have a

decreased capability of withstanding "increased G loads in the head-to-foot direction."[11] Blood perfusion appears to decrease as they begin to feel MS.

The Negative Aspect of Using Drugs to Treat Motion Sickness

In 2004, Buckey et al. conducted a drug study on the effects of Chlorpheniramine on MS in his study titled, "Chlorpheniramine for motion sickness."[12] The study was "a placebo-controlled, double-blind, dose-ranging trial… to establish the most effective dose and the drug's effects on cognition."[12] Subjects had no idea what drug dosage they were receiving. "Eighteen normal, [MS] susceptible subjects either received a placebo, low dose, or high dose" before being centrifuged by off-axis vertical rotation.[12] Each subject went through three trials and received a different dosage of the drug each time they had a new trial. The results showed that the drug was an effective agent against MS because subjects were able to increase the time they spent on off-axis vertical rotation by an average of at least 3 minutes with the low or high dose of the drug.[12] When subjects consumed the drug, it took a longer time for the onset of MS to occur. However, "subjects reported significantly more sleepiness and less alertness with high-dose chlorpheniramine."[12] For people who take an excessive amount of chlorepheniramine, they will encounter the same side effects as other drugs used to treat MS. Therefore, while Buckey concluded that chlorepheniramine could possibly be used as an effective transdermal agent against MS, the results show that there is still the potential that it could cause similar sedative side effects as it predecessors, such as scopolamine, dymendydrinate, promethazine, if the dosage is too high.[12] The current drugs available to treat MS still appear to have the potential to cause sedative side effects.

Summary of Conclusions Based on the Literature

In no single study has there been an attempt to assess the CO or the subject's subjective response to multiple cracking pressures of the ITD. Convertino studied the effects of the ITD on cardiac output and demonstrated that the usage of a TEB could help evaluate changes in CO, but the study was limited to evaluating the subject's CO when using only one cracking pressure, set at -6 cm H_2O.[4, 8] There was also no evaluation done by Convertino on how their subjects felt when using the ITD.[4] The study by Lurie did evaluate multiple cracking pressures of the ITD's on a subject's blood pressures, but the subject's COs were not measured.[3] Also, the subjects that were being studied were pigs.[3] All of their data on how the pigs reacted to the ITD was based on objective assumptions only.[3] It appears that an evaluation of the ITD's effect on CO from multiple cracking pressures has not been done on humans yet. This type of study could give us more information towards our understanding on how the ITD affects human physiology.[3] Also, no study, measuring CO, has had enough subjects to show any statistically significant changes. Rickards study, evaluated people's CO, but their usage of eight subjects did not show any statistically significant changes in CO and did not focus on CO.[7] Considering that Lurie's evaluation of the ITD's effect on a pig's BP from multiple cracking pressures helped them find a cracking pressure, -12 cm H_2O, that increased a pig's BP and not make them appear visibly distressed, there was a possibility that a similar experiment done on humans could lead to the discovery of a cracking pressure that increased their CO and not make them work too hard to breathe, which was usually defined as 6 in the modified Borg scale for perceived exertion.[3, 13]

Evaluating a subject's subjective response, by using the modified Borg scale for perceived exertion, to multiple ITD cracking pressures could give valuable insight on how the cracking pressures of the ITD should be set. As indicated in Idris's study, the amount of power someone needed to use an ITD, with a cracking pressure of -7 cm H_2O, should be well below 80 J/min, which Idris defined as the amount of power needed to have an adequate minute ventilation to perform moderate exercise.[6] In the modified Borg scale for perceived exertion, moderate exertion is listed as a score of 3.[9] Therefore, it could be assumed that the power of breathing required to breathe through an ITD, with a cracking pressure set at -7 cm H_2O, should be less than 3. Lurie indicated that the cracking pressure set on the ITD should cause as little exertion as possible.[2] Therefore, it was assumed that an ideal amount of exertion expended to use the ITD should be less than a modified Borg scale score of 3 because the scale indicates that the subject is only exerting only a slight effort at that point.[10] Since people, who indicate that their score is a 6 on the modified Borg scale, are expected to slow down or stop their current activity, it could be assumed that people who had that same score while breathing on an ITD should stop breathing on it as well.[13] Unfortunately, Idris's study only focused on an ITD with a cracking pressure of -7 cm H_2O and the modified Borg scale was never used to evaluate someone's exertion while breathing through the ITD. The application of the modified Borg scale, on an experiment that evaluates the subject's response to multiple cracking pressures, would allow the subject's sensation of exertion to be quantified and would help indicate which set cracking pressures of the ITD make it tough for human subjects to breathe on it.

As seen in all the previous articles involving the ITD, various cracking pressures were assigned to the ITD's used in the experiments. It had already been established that the ITD does decrease negative intrathoracic pressure, allow its hemodynamic effects to occur without influence from the sympathetic system or vagal withdrawl, and that it could cause at least a 1 L/min increase in cardiac output with an ITD set at a cracking pressure of -6 cm H_2O. However, there seems to be no consensus as to what cracking pressure should be used to cause its cardiac effects. With the exception of Lurie's evaluation of how the multiple cracking pressure settings on the ITD's affected the hemodynamics of the study's pig subjects, only one cracking pressure was used for each study. Unfortunately, there were several cracking pressure settings being used for each of these studies.[3-6] The cracking pressures used in the aforementioned articles were set at -6, -7, -10, and -12 cm H_2O.[3-6] Lurie also suggested cracking pressures between -5 to -15 cm H_2O, but also noted that human subjects had used cracking pressures set up to -35 cm H_2O.[2] The effectiveness, the amount of CO increase, tolerability, and the amount of exertion a subject indicates in accordance to the Borg scale of the different cracking pressures set on the ITD should be compared. Since Lurie's previous study that involved multiple cracking pressures had its subjects breathing on cracking pressures that were -5 cm H_2O apart in magnitude, it was assumed that the cracking pressures evaluated should also be as close to -5 cm H_2O apart in magnitude as possible.[3] Also, Lurie's study had a range of cracking pressures between 0 to -20 cm H_2O.[3] Therefore, it was assumed that the cracking pressures tested should be within that range. By evaluating the CO and the perceived exertion Borg scale score of the subjects using multiple ITD's set at different

cracking pressures, within the range of 0 to -20 cm H_2O, it was believed that a cracking pressure, which increases the cardiac output of its human subjects by 1 L/min and does not make the subject's modified Borg scale for perceived exertion score go above 3, will be identified.

Chapter III

Methods

The study was designed as a single blinded, randomized, and quasi-experimental with repeated measurements. Subjects served as their own controls. The study was conducted with the purpose of finding out what physiological changes can occur while healthy, normotensive individuals breathe on an ITD. It was approved by the IRB as protocol number 2008H012 by expedited review under 45 CFR 46.110(b)(1), see Appendix A.

Objectives of the Study

Objective: To find the cracking pressure, that should be set on an ITD, which would allow someone with healthy normal lungs to experience a maximal amount of CO increase, greater than 1 L/min, without having them felt that they were exerting an effort equivalent to a modified Borg scale for perceived exertion score of 3 or above.

Hypotheses: 1) There would be a statistically significant correlation between the magnitudes of set cracking pressures, BPs, and CO for subjects with normal lungs.

2) Subjects would be able to breathe through a cracking pressure setting of -19 cm H_2O and would not indicate that they had a modified Borg scale for perceived exertion score of 6 or above.

3) There would be a statistically significant correlation between the magnitudes of set cracking pressures and the subject's reported scores based on the modified Borg scale for perceived exertion.

Research Questions: 1) Was there a statistically significant correlation between the magnitudes of set cracking pressures, BP, and CO for subjects with normal lungs?

2) Would subjects be able to breathe through the following cracking pressure settings of 0, -7, -11, -15, and -19 cm H_2O and not indicate that they have a modified Borg scale for perceived exertion score of 6 or above?

3) Was there a statistically significant correlation between the magnitudes of set cracking pressures and the subject's reported scores based on the modified Borg scale for perceived exertion?

Population and Sample

Human subjects were recruited from amongst people residing in Columbus, Ohio by "word of mouth," e-mail, and fliers posted at the School of Allied Medical Professions during the summer of 2008. On the fliers and e-mails, see Appendix C, it was noted that a research project was being conducted on people who were 18 or older, healthy, nonsmoking, nonpregnant, and capable of walking for 20 minutes. Also, the volunteers that qualified for the study would be eligible to receive one of two $25.00 VISA debit cards by raffle. People willing to volunteer for the study were requested to call or e-mail the contact information listed on the fliers and e-mails to indicate their interest.

To qualify to participate in the study, volunteers were to be above the age of 18 and physically healthy. They were considered to be physically healthy if they indicated that they were normotensive, nonpregnant individuals who had no reported history of cardiopulmonary abnormalities during their screenings. When a volunteer called or sent an e-mail indicating their interest in becoming a subject, they were sent a list of screening questions. They were asked:

1. Are you at least 18 years old?
2. Have you ever had any health problems with your heart or lungs?
3. Do you smoke?
4. Are you pregnant or do you suspect that you may be pregnant?
5. Have you had any trouble walking for twenty minutes?

When the volunteer answered, “Yes” for the first question and, “No” for the rest of the questions, the subject passed the initial screening. They were then scheduled to come into the lab in room 438 Atwell Hall, sent a consent form and sent an information sheet explaining the study procedures.

At the lab, volunteers underwent a second screening. After briefly explaining the experiment and acquiring written consent, a pulse oximeter, BP cuff, and 13 leads from an EKG and non-invasive CO monitor (ICG BioZ module) were placed on the volunteers to check their initial measurements before the start of experimentation. Also, the volunteers were asked their age, height, and weight because those variables affected the outcome of the measurements that were calculated by the ICG BioZ Module. The volunteers had to have a BP between 90/60 to 130/85, an arterial oxygen saturation level of at least 95%, a HR between 60 to 100 beats/min, a CO between 3 to 6 Liters/min, and a RR between 12 to 20 breaths/min in order to continue the experiment. At this point volunteers were considered “subjects” that qualified for the study. Qualified subjects were instructed to keep on the measuring devices used to screen them when the experiment started.

Methodology

At the start of the study, subjects were instructed to put on nose clips and form a tight seal with their lips around the mouthpiece of a “baseline” ITD for 2 minutes. This baseline ITD offered no resistance. It had a cracking pressure of 0 cm H_2O. However, subjects were unaware of the setting of this ITD and were encouraged to continue

breathing though the device despite any resistances they might have felt. While the subjects breathed on this baseline ITD, their BP, arterial oxygen saturations, RR, HR, and CO were continuously monitored. After 2 minutes, these measurements were recorded from the ICG BioZ Module. In addition to these recorded measurements, subjects verbally indicated their modified Borg Scale for Perceived Exertion score. This score, along with the setting of the ITD, was written on the sheet that contained the recorded measurements.

After the subjects' measurements were recorded from this baseline, subjects were then instructed to randomly select a pre-set ITD to breathe on for 2 minutes. The ITDs had cracking pressures pre-set to either -7,-11, -15, or -19 cm H_2O. The subjects were unaware of the settings of these ITDs. Since the settings of these ITDs were based on the different colored pieces of electrical tape that were put on them, only the investigator knew what the colors meant. The subjects blindly selected one of these ITDs from a box and started to breathe on it whenever they were ready. They were given time to get a drink of water or rest before they started breathing on the ITD they selected. Subjects breathed on this randomly selected device for at least 2 minutes while having their BP, arterial oxygen saturations, RR, HR, and CO continuously monitored. These measurements were the same physiological measurements that were recorded while the subjects were breathing on the baseline ITD. On occasion, some subjects were instructed to breathe on this randomly selected ITD for more than 2 minutes when there was a need to wait for the BP cuff to inflate or adjust some of the EKG/ICG BioZ Module leads. After a minimum of 2 minutes, the measurements were recorded, their verbally indicated

Borg score was written, and the setting of the ITD was recorded. Also, the used ITD was set aside and no longer available for selection.

After breathing on each ITD, subjects were instructed to breathe on the baseline ITD again until their physiological measurements were the same as their baseline values. Although this time was originally set up to be a 2 minute period, sometimes subjects were instructed to breathe on the baseline ITD for a longer period of time to allow more time for their body to adjust back towards its baseline measurements. Once the subjects' Borg scores and physiological measurements returned near their baseline values for a minimum of 2 minutes, their physiological measurements were recorded, subjects were then asked to repeat the process of selecting a random ITD from the box. The processed is summarized in Table 2.

Table 2. Experiment Timeline.

2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	2 min
Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline

Instrumentation

The ICG BioZ Module, see Figure 1, is a non-invasive cardiac output monitor that uses a combination of the EKG and TEB devices to measure a subject's CO. It measures a subject's CO non-invasively.

Figure 1. ICG BioZ Module.

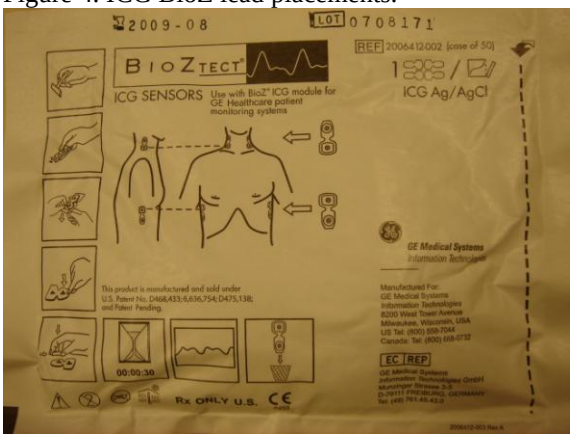
Thirteen electrical leads were placed on a subject's neck and chest. The EKG had 5 leads that need to be attached to the chest, see Figures 2. These leads were used to measure HR and RR. The HR was used to calculate the CO. The 8 TEB leads were used to detect SV of the heart, see Figure 3. The ICG BioZ module required the leads to be

Figure 2 EKG Leads.

placed on the neck and ribcage, see Figure 4. The SV, which was determined by

Figure 3. ICG BioZ leads.

Figure 4. ICG BioZ lead placements.



averaging the SV acquired from a set number of cardiac cycles, were used to calculate the subject's CO.[4] The CO was calculated by multiplying the subject's HR times their averaged SV.[8]

In addition to the ICG BioZ Module, two other instruments were added to the apparatus to measure BP and SpO_2. The type of blood pressure cuff used was a self-inflating BP cuff that could be activated when needed, as seen in Figure 5.

Figure 5. Self inflating blood pressure cuff.

The pulse oximeter, as seen in Figure 6, was used to measure the subject's arterial blood saturation and HR. It used a padded clip to attach to the subject's finger.

Figure 6. Pulse Oximeter.

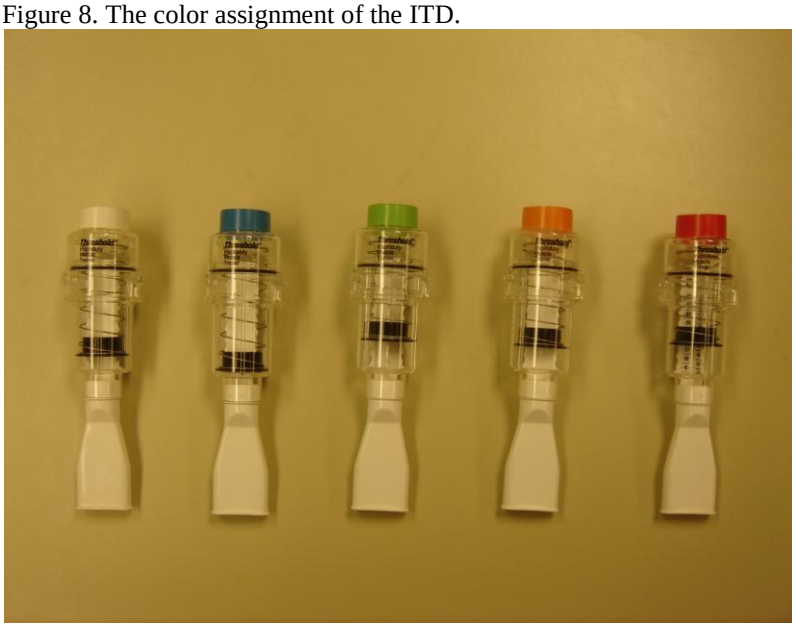
With the usage of an LED light and photoreceptors, it was able to give an estimation of oxygen saturation in arterial blood.

The ITD, as seen in Figure 7, was used to provide variable inspiratory cracking pressures to the subjects. These particular ITDs were marketed as inspiraratory muscle trainers. It used a spring and diaphragm to impede a person's inhalation until they created

Figure 7. The ITD designed by Threshold.

a certain amount of subatmospheric intrathoracic pressure in their lungs. The cracking pressure on the ITD could be adjusted to different magnitudes of cracking pressures from -7 cm H_2O to -41 cm H_2O. Cracking pressures were marked in increments of two, limiting the possible cracking pressure settings the ITD could be set on. The cracking pressure settings of the ITD that were within the range of 0 to -20 cm H_2O and had a separation somewhat close to 5 cm H_2O were determined to be -7, -11, -15, and -19 cm H_2O. The settings of each ITD were verified using a Negative Inspiratory Force meter and a 3L syringe. The settings of the ITDs were assigned to different colors, as shown in Figure 8. White = baseline 0, Blue = -7, Green = -11, Orange = -15, and Red = -19.

Figure 8. The color assignment of the ITD.



The modified Borg Scale for Perceived Exertion, as seen in Table 3, was used to assess the effort subjects felt that they have to exert while breathing through the ITD. It was a scale that had been commonly used to rate "how [the] whole body [felt] in response to an activity."[10] It is a 12 point scale that ranged from a score of 0 to a score of 10. Only 10 of

the 12 points were labeled with words indicating a perceived exertion status. A rating of 0 indicated that the subjects felt that they did not have to exert any effort at all while breathing through the ITD. A rating of 10 indicated that the subjects felt that they had to exert so much effort to breathe through the ITD that they just could not use it anymore.

Table 3. The Modified Borg Scale for Perceived Exertion

0	No effort
0.5	Very, very slight effort (just noticeable)
1	Very slight effort
2	Slight effort
3	Moderate effort
4	Somewhat strong effort
5	Strong effort
6	Very strong effort
7	
8	
9	Very, very strong effort (almost maximal effort)
10	Maximal effort

Data Analysis

To identify the characteristics of the sample, the means and standard deviations of the subjects' physiological variables were calculated and compared to normal values for age and gender.

To determine if there was a significant relationship or difference between Borg scores and cracking pressures, a Pierson correlation coefficient was calculated and an

analysis of variance was performed. Also, the percentage of Borg scores over "very strong effort," was calculated to see if there was a variable difference between the cracking pressures as they became more negative. Any significant differences were evaluated with a Tukey's Post-hoc.

To determine if there was a significant relationship or difference between cracking pressures and the physiological variables a Pierson correlation coefficient was calculated and an analysis of variance (ANOVA) was performed. During the study, if the ICG BioZ Module was incapable of making a proper reading, the cardiac output evaluated at the time was not included along with the other measurements during that particular time.

Chapter IV

Description of the Study

Introduction

Problem Statement

Within the last five years, several studies have been conducted assessing the possibility of using induced negative intra-thoracic pressure to increase cardiac output (CO). Subatmospheric intrathoracic pressure, which is referred to as "negative pressure," naturally occurs within a person's thoracic cavity when they take an inspiration.[1] Almost everyone must create a substantial amount of negative pressure within their thoracic cavity to allow airflow into their lungs. However, this negative intra-thoracic pressure can be increased to a greater intensity by adding some resistance to a person's inspiration.[2] It is believed that with this technique of inducing an increase in negative pressure within the thoracic cavity, blood return to the heart will increase.[3] Because the heart receives more blood, the heart contracts more forcefully, due to the Frank Starling Mechanism, which increases its cardiac output.[1]

It has been suggested that it may be possible to use negative intrathoracic pressure to treat people who are in a state of hypovolemia or hypotension.[3-5] People, who are in these conditions, typically experience poor blood circulation within a short period of time. By temporarily increasing a person's CO with the usage of induced negative intrathoracic pressure, it is believed that the effects of hypovolemia or hypotension will be delayed.[4]

Researchers have suggested that negative intrathoracic pressure should be induced within these people with the aid of an impedance threshold device (ITD).[3-5]

The ITD is a tool designed to temporarily increase the CO and stroke volume (SV) of someone's heart by impeding their breathing for a short period of time each time they inhale through the device.[2-4] Initially, when its user inhales through the device, an air seal within the ITD will prevent air from entering into their lungs.[2-4] However, since the user's lungs are continually expanding, the negative pressure decreases within their lungs. Eventually, the decreasing negative pressure within the user's lungs will become low enough to cause the air seal within the ITD to crack open, allowing air to flow into their lungs.[2-4] Each ITD is set to allow air to flow in at a specific "cracking pressure," which is the term assigned to describe the amount of negative pressure one's lungs must create before the ITD will "crack open" its air seal.[2-4] Typically a person will only need to use a fraction of their generated negative pressure to overcome this cracking pressure.

Despite the amount of research being done on the possible benefits of the ITD, there has been no clear standard as to what cracking pressures the ITD needs to be in order to enable its effects on CO and SV. As of now, we only know that an ITD should be set within a certain range of cracking pressures. For example, an article by Lurie suggests that the lowest possible cracking pressure that induces its hemodynamic effects should be used due to the possibility of operator error.[2] However, in his conclusion he does not leave a decisive value as to what the cracking pressure should be and instead just suggests a pressure range of -5 to -15 cm H_2O.[2] Several other studies have been using an ITD with a cracking pressure of -7 cm H_2O on people, but it had also been determined

that people were willing to tolerate pressures of up to -20 cm H_2O.[2-4] Currently, there are several different versions of the ITD being sold for different situations that occur within the hospital, with cracking pressures of -7, -10, and -16 cm H_2O, but no baseline has been set as to what cracking pressure will allow a person with healthy, normal lungs to increase their CO and not experience a sensation of having to work hard to breathe.

The objectives of this study were to find the cracking pressure, that should be set on an ITD, which would allow someone with healthy normal lungs to experience a maximal amount of acute CO increase, greater than 1 L/min, without having them feel that they are exerting an effort equivalent to a modified Borg scale for perceived exertion score of 3 or above.

To accomplish the objectives, the following three hypotheses were tested; 1) There would be a statistically significant correlation between the magnitudes of set cracking pressures, blood pressures (BP), and CO for subjects with normal lungs. 2) Subjects would be able to breathe through a cracking pressure setting of -19 cm H_2O and would not indicate that they have a modified Borg scale for perceived exertion score of 6 or above. 3) There would be a statistically significant correlation between the magnitudes of set cracking pressures and the subject's reported scores based on the modified Borg scale for perceived exertion.

This study was also conducted with the purpose of finding out what physiological changes would occur while healthy, normotensive individuals breathed on an ITD, which lead to the following three questions; 1) Was there a statistically significant correlation

between the magnitudes of set cracking pressures, BP, and CO for subjects with normal lungs? 2) Would subjects be able to breathe through the following cracking pressure settings of 0, -7, -11, -15, and -19 cm H_2O and not indicate that they had a modified Borg scale for perceived exertion score of 6 or above? 3) Would there a statistically significant correlation between the magnitudes of set cracking pressures and the subject's reported scores based on the modified Borg scale for perceived exertion?

Methods

Subjects

Human subjects were recruited from amongst people residing in Columbus, Ohio by "word of mouth," e-mail, and fliers posted at the School of Allied Medical Professions during the summer of 2008. To qualify for participation in the study, volunteers were to be 18 or older, healthy, nonsmoking, nonpregnant, and capable of walking for 20 minutes. Subjects had to give written consent before having their physiological values measured. A pulse oximeter, BP cuff, and 13 leads from an EKG and non-invasive CO monitor (ICG BioZ module) were placed on the volunteers to check their initial measurements before the start of experimentation. Also, the volunteers were asked their age, height, and weight because those variables affected the outcome of the measurements that were calculated by the ICG BioZ Module. The volunteers had to have a BP between 90/60 to 130/85, an arterial oxygen saturation level of at least 95%, a heart rate (HR) between 60 to 100 beats/min, a CO between 3 to 6 Liters/min, and a respiratory rate (RR) between 12 to 20 breaths/min in order to continue the experiment. Qualified subjects were instructed

to keep on the measuring devices used to screen them when the experiment started. The experimental procedures of this study on human subjects were reviewed and approved by the Biomedical Institutional Review Board of The Ohio State University.

Protocol

The study was designed as a single blinded, randomized, and quasi-experimental with repeated measurements. Subjects served as their own controls.

At the start of the study, subjects were instructed to put on nose clips and form a tight seal with their lips around the mouthpiece of a "baseline" ITD for two minutes. This baseline ITD offered had a cracking pressure of 0 cm H_2O. However, subjects were unaware of the setting of this ITD and were encouraged to continue breathing though the device despite any resistances they might have felt. While the subjects breathed on this baseline ITD, their BP, arterial oxygen saturations, RR, HR, cardiac index (CI) and CO were continuously monitored. After 2 minutes, these measurements were recorded from the ICG BioZ Module. In addition to these recorded measurements, subjects verbally indicated their modified Borg Scale for Perceived Exertion score. This score, along with the setting of the ITD, was written on the sheet that contained the recorded measurements.

After the subjects' measurements were recorded from this baseline, subjects were then instructed to randomly select a pre-set ITD to breathe on for 2 minutes. The ITDs had cracking pressures pre-set to either -7,-11, -15, or -19 cm H_2O. The subjects were unaware of the settings of these ITDs. Since the settings of these ITDs were based on the different colored pieces of electrical tape that were put on them, only the investigator

knew what the colors meant. The subjects blindly selected one of these ITDs from a box and started to breathe on it whenever they were ready. Subjects breathed on this randomly selected device for at least 2 minutes while having their BP, arterial oxygen saturations, RR, HR, and CO continuously monitored. On occasion, some subjects were instructed to breathe on this randomly selected ITD for more than 2 minutes when there was a need to wait for the BP cuff to inflate or adjust some of the EKG/ICG BioZ Module leads. After a minimum of 2 minutes, the measurements were recorded, their verbally indicated Borg score was written, and the setting of the ITD was recorded. Also, the used ITD was set aside and no longer available for selection.

After breathing on each ITD, subjects were instructed to breathe on the baseline ITD again for a 2 minute period. Sometimes, subjects were instructed to breathe on the baseline ITD for a longer period of time to allow more time for the BP cuff to inflate and get an accurate reading. After 2 minutes, their physiological measurements were recorded. Subjects were then asked to repeat the process of selecting a random ITD from the box. The processed is summarized in Table 1.

Table 1. Experiment Timeline.

2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	≥ 2 min	2 min
Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline	Randomly assigned cracking pressure	Baseline

Measurement of Physiological Variables

The ICG BioZ Module was used to measure a subject's cardiac output non-invasively with a combination of the EKG and thoracoelectric bioimpedance (TEB) devices. Thirteen electrical leads were placed on a subject's neck and chest. The EKG had 5 leads that need to be attached to the chest. These leads were used to measure HR and RR. The HR was used to calculate the CO. The 8 TEB leads were used to detect SV of the heart. The ICG BioZ module required the leads to be placed on the neck and ribcage. The SV, which was determined by averaging the SV acquired from a set number of cardiac cycles, were used to calculate the subject's CO.[4] The CO was calculated by multiplying the subject's HR times their averaged SV.[9]

In addition to the ICG BioZ Module, 2 other instruments were added to the apparatus to measure BP and SpO_2. The type of BP cuff used was a self-inflating BP cuff that could be activated when needed. The pulse oximeter was used to measure the subject's arterial blood saturation and HR. It used a padded clip to attach to the subject's finger. With the usage of an LED light and photoreceptors, it was able to give an estimation of oxygen saturation in arterial blood.

The Impedance Threshold Device

The ITD, see Figure 1, was used to provide variable inspiratory cracking pressures to the subjects. These particular ITDs were marketed as inspiraratory muscle trainers. It used a spring and diaphragm to impede a person's inhalation until they created certain amount of subatmospheric intrathoracic pressure in their lungs. The cracking pressure on the ITD could be adjusted to different magnitudes of cracking pressures from

-7 cm H_2O to -41 cm H_2O. Cracking pressures were marked in increments of 2, limiting the possible cracking pressure settings the ITD could be set on. The cracking pressure settings of the ITD that were within the range of 0 to -20 cm H_2O and had a separation somewhat close to 5 cm H_2O were determined to be -7, -11, -15, and -19 cm H_2O. The settings of each ITD were verified using a Negative Inspiratory Force meter and a 3L syringe. The settings of the ITDs were assigned to different colors. White = baseline 0, Blue = -7, Green = -11, Orange = -15, and Red = -19.

Figure 1. The ITD designed by Threshold.

Measurement of Perceived Exertion

The modified Borg Scale for Perceived Exertion, as seen in Table 2, was used to assess the effort subjects felt that they have to exert while breathing through the ITD. It is a scale that has been commonly used to rate "how [the] whole body [felt] in response to an activity."[10] It is a 12 point scale that ranged from a score of 0 to a score of 10. Only 10 of the 12 points were labeled with words indicating a perceived exertion status. A rating of 0 indicated that the subjects felt that they did not have to exert any effort at all while

breathing through the ITD. A rating of 10 indicated that the subjects felt that they had to exert so much effort to breathe through the ITD that they just could not use it anymore.

Table 2. The Modified Borg Scale for Perceived Exertion

0	No effort
0.5	Very, very slight effort (just noticeable)
1	Very slight effort
2	Slight effort
3	Moderate effort
4	Somewhat strong effort
5	Strong effort
6	Very strong effort
7	
8	
9	Very, very strong effort (almost maximal effort)
10	Maximal effort

Data Analysis

To identify the characteristics of the sample, the means and standard deviations of the subjects' physiological variables were calculated and compared to normal values for age and gender.

To determine if there was a significant relationship or difference between Borg scores and cracking pressures, a Pierson correlation coefficient was calculated and an analysis of variance was performed. Also, the percentage of Borg scores over "very strong effort," was calculated to see if there was a variable difference between the

cracking pressures as they became more negative. Any significant differences were evaluated using a Tukey's Post-hoc.

To determine if there was a significant relationship or difference between cracking pressures and the physiological variables a Pierson correlation coefficient was calculated and an analysis of variance (ANOVA) was performed. During the study, if the ICG BioZ Module was incapable of making a proper reading, the CO evaluated at the time was not included along with the other measurements during that particular time.

Results

Twenty-five individuals volunteered, 23 subjects qualified, and 21 completed the study. The demographic and physiological variables of the subjects (n = 21), breathing through an ITD set at a cracking pressure of 0 cm H_2O, are described in Table 3.

Table 3. Demographic and physiological variables of the subjects breathing on an ITD set at 0 cm H_2O.

Physiological Variables (Units)	Mean	Std. Deviation
Age (years)	23.2	3.3
Height (inches)	67.6	3.1
Weight (lbs.)	152.2	24.2
Heart Rate (beats/min)	67.6	10.0
Respiratory Rate (breaths/min)	17.7	5.6
Systolic Blood Pressure (mm Hg)	113.1	12.4
Diastolic Blood Pressure (mm Hg)	66.9	5.2
Pulse Pressure (mm Hg)	46.3	10.8
Mean Arterial Pressure (mm Hg)	82.3	6.6
SpO2 (%)	98.1	1.4
Cardiac Index (L/min/m^2)	2.7	0.4
Cardiac Output (L/min)	4.8	0.9

During the experiment, each subject breathed on a total of 5 different cracking pressure settings and declared their breathing effort using the Borg Scale for Perceived Exertion. Table 4 presents the Pearson correlation coefficient between cracking pressures (set at -7, -11, -15, and -19 cm H_2O) and Borg scale scores. There was a statistically significant strong negative correlation between cracking pressures and Borg scale scores

Table 4. Correlation between Cracking pressures and Borg scale scores.

Pearson correlation	-.814**
Sig. (2-tailed)	.000
N	105

**. $p < 0.01$ level (2-tailed).

($r = -0.814$, $p < 0.01$). Therefore, subjects indicated that they felt they had to exert more effort as the cracking pressure became more negative.

The means and standard deviations of the Borg scale scores for each cracking pressure are provided in Table 5. The means for both the cracking pressures of 0 cm H_2O and -7 cm H_2O were each significantly different from the means of the four other cracking pressures ($p < 0.05$). Also, there were statistically significant differences of the means between the cracking pressures of -11 cm H_2O and -19 cm H_2O ($p < 0.05$). There were no statistically significant differences between the means of -11 cm H_2O and -15 cm H_2O or -15 cm H_2O and -19 cm H_2O. Some subjects reported Borg scale scores of 6 or greater while they were breathing on cracking pressures set at -11 cm H_2O or lower, as shown in Table 5. The percentage of subjects indicating a score of 6 or greater increased as the cracking pressures became more negative. As the magnitude of the cracking pressures on the ITD increased, more subjects reported the feeling of having to exert a "very strong effort" or greater.

Table 5. Means and Percentages of reported Borg scale scores greater than 6.

Cracking pressure ($cm H_2O$)	Mean	SD	% Borg scale score < 6 (N)	% Borg scale score ≥ 6 (N)
0	0.26[a]	0.37	100 (21)	
-7	2.69[a]	1.17	100 (21)	
-11	3.91[b]	1.61	81 (17)	19 (4)
-15	4.66	1.58	71 (15)	29 (6)
-19	5.79[b]	1.64	57 (12)	43 (9)

a. These means were different from the means of the 4 other cracking pressures ($p < 0.05$).
b. These means were different from each other ($p < 0.05$).

Table 6 presents the Pearson correlation coefficients between cracking pressures and the measured physiological variables. There were no statistically significant correlations between the cracking pressures and any of the physiological variables measured. The physiological variables were not likely affected by changes in cracking pressures. Although there was the possibility of 105 physiological variables and Borg scale scores that could be measured, the n for CI and CO was 99 due to the occasional misreading of the non-invasive CO monitor.

Table 6. Correlation between Cracking pressures and Physiological variables.

	HR	RR	SBP	DBP	PP	MAP	SpO2	CI	CO
Pearson correlation	-.108	.015	.107	.098	.065	.118	-.113	-.087	-.055
Sig. (2-tailed)	.272	.878	.276	.321	.507	.232	.251	.393	.589
N	105	105	105	105	105	105	105	99	99

Table 7 compares the means of the physiological variables for each cracking pressure. An ANOVA analysis on these means indicated that there were no statistically significant differences between the means of any physiological variables while subjects were breathing on the 5 cracking pressures.

Table 7. ANOVA comparison of Cracking pressures and Physiological variables.

Cracking pressure (cm H_2O)	HR	RR	Systolic BP	Diastolic BP	PP	MAP	SpO2	CI	CO
0	67.6 (10.0)	17.7 (5.6)	113.1 (12.4)	66.9 (5.2)	46.3 (10.8)	82.3 (6.6)	98.1 (1.4)	2.7 (0.4)	4.8 (0.9)
-7	70.0 (9.7)	16.5 (5.4)	109.4 (12.3)	63.3 (5.8)	46.1 (10.9)	78.7 (6.8)	98.0 (1.5)	2.8 (0.4)	5.0 (0.9)
-11	69.6 (10.2)	14.9 (4.7)	108.1 (14.2)	63.5 (6.5)	44.6 (12.0)	78.4 (8.0)	98.6 (1.4)	2.7 (0.3)	4.9 (0.7)
-15	70.3 (9.8)	17.5 (7.7)	110.0 (12.1)	65.5 (7.6)	44.5 (11.5)	80.3 (7.6)	98.2 (1.5)	2.7 (0.3)	5.0 (0.8)
-19	71.0 (9.6)	17.2 (8.8)	108.4 (14.0)	63.9 (8.3)	44.5 (10.9)	78.8 (9.2)	98.5 (1.2)	2.8 (0.3)	5.0 (0.7)

Reported as Mean (SD).

Discussion

There are multiple scenarios when a spontaneously breathing person can experience a sudden onset of hypotension. Acute hypotension has been shown to correlate with individuals experiencing orthostatic intolerance or motion sickness.[5, 11] Recovery or delay from the hypotension that occurs during these scenarios can "[delay] the onset of presyncopal symptoms and [help people maintain] consciousness."[7] In this study, it was assumed that delaying acute hypotension would effectively decrease the severity of its symptoms. The current means available to deal with acute hypotension in normovolemic, normotensive, spontaneously breathing individuals are to treat its symptoms, which usually involve pharmaceuticals.[12] Sailors or aviators take drugs to treat their motion sickness.[12] However, the drugs that the sailors and aviators take to treat their motion sickness can cause drowsiness.[12] Therefore, finding a cheap, natural, and effective way to delay acute hypotension, before its symptoms occur, is highly desirable.

The objectives were not met in this study. However, several assumptions could be made about the ITD from the results of this study.

Since previous studies have shown that an ITD can increase CO, it was assumed that the ITD would have a prophylactic effect on acute hypotension.[7] However, in order for this to be true, the ITD would have to demonstrate the capability of raising CO within a short time period. Lurie's study on the acute effects of the ITD on normovolemic and hypovolemic pigs demonstrated that two minutes was enough time to cause a change in BP.[3] While Lurie's subjects were breathing on the ITD, their BP increased within a 2 minute interval.[3] Lurie's results contradict the results of this study, which show that there are no acute physiological changes associated the ITD while an individual is breathing on it for a 2 minute time period. There were no statistically significant relationships between negative inspiratory pressure and HR, Systolic BP, Diastolic BP, MAP, SpO2, CI, or CO. A change in the cracking pressures of the ITDs were shown to only affect the amount of exertion one felt while breathing on an ITD. Subjects felt they were exerting more effort as the cracking pressures of their ITDs became more negative. The different methods in acquiring BP could be a possible reason for the contrasting conclusions. Lurie's study measured BP invasively and continuously via an aortic pressure transducer.[3] An automated BP cuff was used to measure BP in this study. The fact that an aortic pressure transducer can measure BP continuously and more accurately than a BP cuff may have helped Lurie detect acute changes in BP more frequently. However, Convertino was able to detect changes in BP in his subjects using an inflatable BP cuff, which makes it likely that another factor is determines whether acute changes in BP can be detected.[4]

It may require more time for the ITD to cause physiological changes in humans compared to pigs. The results of our study and Convertino's study evaluating the hemodynamics of 20 healthy, normotensive, nonsmoking men and women breathing on an ITD suggests that it takes longer than 2 minutes for the effects of the ITD to occur within normovolemic, normotensive, spontaneously breathing human beings.[4] Convertino found that there was a statistically significant increase in SBP, DBP, HR, and CO using an ITD set at a cracking pressure of -6 cm H_2O.[4] However, despite the fact that the subjects in our study were breathing on ITDs set at even more negative pressures than -6 cm H2O, Convertino's results were not replicated. Even though our subjects were clearly feeling like they had to exert more effort as the cracking pressures became more negative, their physiological variables were not different from their baseline values. There is no relationship between a "very strong effort" Borg score and changes in our physiology. This suggests that humans may feel like they are exerting an extraordinary amount of effort to utilize the device, but it will not necessarily cause any instantaneous physiological changes. Also, the different results may be attributed to the differences in methodology, between our study and Convertino's study, on the amount of time the subjects breathed on the ITD. In Convertino's study, the subjects breathed on the ITD for 14 minutes.[4] The amount of time Convertino made his subjects breathe on the ITD was 7 times longer than the 2 minutes minimum our subjects had to do. As long as the cracking pressure is providing a resistance of -6 H_2O, the magnitude of the cracking pressure settings of the ITD does not appear to be a major factor in determining the effectiveness

of the ITD, it seems that the amount of time someone breathes on an ITD plays a more influential role on its effectiveness to alter human physiology.

Extending the amount of time a subject breathes on an ITD in our subjects from 2 minutes to 3 minutes may be all that is needed for the ITD to cause acute changes in our physiology. Cooke had his subjects breathe on a -7 cm H_2O ITD at a constant rate of 15 breaths per minute for 3 minutes while staying in a supine position.[6] These conditions caused an increase in arterial pressure, HR, and mean cerebral blood flow velocity (CBFV) within their subjects.[6] However, this also brings more questions because the subjects in Cooke's studies were not spontaneously breathing. Is there a significant difference between the effects of the ITD on people are spontaneously breathing on it in compared to the people who are breathing on it at a controlled RR. Also, Cooke was measuring BP continuously, which suggests that our usage of an inflatable BP cuff limited our ability to detect some of the acute changes of BP that could have been cause by the ITD. In order to detect any physiological changes of BP on someone who is breathing on an ITD for 2 to 3 minute intervals, the results of our study, Lurie's study, and Cooke's study suggests that it is necessary to use a BP monitoring device that measures BP continuously.

Limitations

The focus of our study was not the amount of time it took for an ITD to effectively influence our physiology. Instead, we focused on evaluating how the magnitudes of different ITD cracking pressure settings would affect our subjects. Also,

by not measuring BP continuously, acute changes in BP may have not been detected during each time interval. A known standard in the amount of time it takes for the ITD to cause acute physiological changes while measuring BP continuously could better help us determine if the cracking pressure magnitude of the ITD really does have a significant role in determining the effectiveness of the device.

Conclusion

Our results lead to the conclusion that while the ITD can make normovolemic, normotensive, spontaneously breathing individuals feel like they are exerting more effort as the magnitude of its cracking pressure becomes more negative, there is no evidence to support that it causes any physiological changes within a 2 minute time period. The amount of time a subject spends breathing on an ITD, the ability of the investigator to measure BP continuously, and the way a subject breathes on the ITD appear to be the main factors in detecting its acute physiological effects. Therefore, it does not seem appropriate to expect that the ITD will provide instant relief for humans experiencing acute hypotension if they breathe on it for only a short period of time.

ACKNOWLEDGEMENTS

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Chapter V

Summary and Conclusions

Our results lead to the conclusion that while the ITD can make normovolemic, normotensive, spontaneously breathing individuals feel like they are exerting more effort as the magnitude of its cracking pressure becomes more negative, there is no evidence to support that it causes any physiological changes within a 2 minute time period. The amount of time a subject spends breathing on an ITD, the ability of the investigator to measure BP continuously, and the way a subject breathes on the ITD appear to be the main factors in detecting its acute physiological effects. There is no relationship between a "very strong effort" Borg score and changes in our physiology. Humans may feel like they are exerting an extraordinary amount of effort to utilize the device, but it will not necessarily cause any instantaneous physiological changes. Therefore, it does not seem appropriate to expect that the ITD will provide instant relief for humans experiencing acute hypotension if they breathe on it for only a short period of time.

The lack of physiological changes that occurred within the subjects while they were breathing on the ITD suggests that it might have been beneficial to increase the amount of time the subjects breathed on the ITD. While evaluating the articles, there were no standards as to how much time was needed for the ITD to cause physiological changes within a human being. Considering how Convertino and Cooke were able to cause physiological changes by putting people on a -6 cm H_2O ITD for 14 minutes and three minutes respectively, it may have been to ask the subjects to breathe on the ITD for

those lengths of time. However, Lurie's study had convincing evidence that the ITD could cause acute physiological changes could be caused within a 2 minute time period.[2] Also, more negative cracking pressures of -7 cm H_2O, -11 cm H_2O, -15 cm H_2O, and -19 cm H_2O were being used in our study. Nevertheless, there appeared to be no relationship between the magnitude of the cracking pressures and changes in physiology. Clearly, it seems apparent that the amount of time someone breathed on an ITD is even more important than the magnitude of the ITD cracking pressure. Knowing this fact, conducting a study, which evaluated the amount of time it took for an ITD to cause physiological changes, probably would have been the more logical study to do before this study so that a standard amount of time necessary to cause physiological changes could be indentified and used for this study.

The completion of this study, "The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion" mostly left us asking more questions. If the amount of time someone breathes on the ITD determines how effective an ITD is, how much time is necessary to cause these changes? Why are there no time or RR standards on how to effectively use this device? Does the magnitude of the cracking pressure still play a role in determining the effectiveness of the ITD if it is used for longer periods of time? This study leads to the conclusion that more tests need to be done to standardize the usage of this ITD.

Appendix A

Biomedical Institutional Review Board

Office of Responsible Research Practices
300 Research Foundation
1960 Kenny Road
Columbus, OH 43210-1063

Phone (614) 688-8457
Fax (614) 688-0366
www.orrp.osu.edu

April 1, 2008

Protocol Number:	2008H012
Protocol Title:	THE EVALUATION OF MULTIPLE IMPEDANCE THRESHOLDS ON CARDIAC OUTPUT AND PERCEIVED EXERTION, F. Herbert Douce, Richard D. Ha, Phillip D. Hoberty, School of Allied Medical Professions
Type of Review:	Initial Review – expedited
IRB Staff Contact:	Nina Jackson 614-247-1557 jackson.940@osu.edu

Dear Dr. Douce,

The Biomedical IRB **APPROVED BY EXPEDITED REVIEW** the above referenced protocol. The Board was able to provide expedited approval under 45 CFR 46.110(b)(1) because the research presents minimal risk to subjects and qualifies under the expedited review category(s) listed below.

Date of IRB Approval:	**March 27, 2008**
Date of IRB Approval Expiration:	**February 18, 2009**
Expedited Review Category:	**4**

If applicable, informed consent (and HIPAA research authorization) must be obtained from subjects or their legally authorized representatives and documented prior to research involvement. The IRB-approved consent form and process must be used. Changes in the research (e.g., recruitment procedures, advertisements, enrollment numbers, etc.) or informed consent process must be approved by the IRB before they are implemented (except where necessary to eliminate apparent immediate hazards to subjects).

This approval is valid for **one year** from the date of IRB review when approval is granted or modifications are required. The approval will no longer be in effect on the date listed above as the IRB expiration date. A Continuing Review application must be approved within this interval to avoid expiration of IRB approval and cessation of all research activities. A final report must be provided to the IRB and all records relating to the research (including signed consent forms) must be retained and available for audit for at least 3 years after the research has ended.

It is the responsibility of all investigators and research staff to promptly report to the IRB any serious, unexpected and related adverse events and potential unanticipated problems involving risks to subjects or others.

This approval is issued under The Ohio State University's OHRP Federalwide Assurance #00006378.

All forms and procedures can be found on the ORRP website – www.orrp.osu.edu. Please feel free to contact the IRB staff contact listed above with any questions or concerns.

Karla Zadnik, OD, PhD, Chair
Biomedical Institutional Review Board

Appendix B

INITIAL REVIEW OF HUMAN SUBJECTS RESEARCH

The Ohio State University Institutional Review Boards

Office of Responsible Research Practices (ORRP)
300 Research Foundation Building, 1960 Kenny Road, Columbus, OH 43210
Phone: (614) 688-8457 Fax: (614) 688-0366 www.orrp.osu.edu

OFFICE USE	DATE RECEIVED:	DATE VERIFIED COMPLETE:	OSU PROTOCOL NUMBER:

1. PROJECT TITLE

The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion

2. INSTITUTIONAL REVIEW BOARD

Select the Board to review this research:
Final Board assignment is determined by ORRP.

- ☐ Behavioral and Social Sciences
- ☒ Biomedical Sciences
- ☐ Cancer

3. PRINCIPAL INVESTIGATOR (or Advisor) - see Qualifications for service as a PI

Name (Last, First, MI):	**Douce, F., Herbert**	Degree(s):	**MS**
University Academic Title:	**Associate Professor**	College (TIU):	**Medicine**
Department Name (TIU):	**Allied Medical Professions**	Department # (TIU):	**2504**
Campus Mailing Address:	**431 Atwell Hall** **453 W. Tenth Avenue** **Columbus, OH 43210**	OSU ID Number (8 digits):	**74041286**
E-mail:	**Herb.douce@osumc.edu**	Fax:	**614-292-0210**
Phone:	**614-292-8445**	Emergency phone:	**614-370-2962**

4. CO-INVESTIGATOR(S)

Are there any OSU Co-Investigators on this protocol?
Original signatures of Co-Investigator(s) are required.

- ☒ Yes → Complete **Appendix A1**
- ☐ No

5. OTHER KEY PERSONNEL

Are there any OSU key personnel on this protocol?

- ☐ Yes → Complete **Appendix A2**
- ☒ No

Key personnel are defined as individuals who participate in the design, conduct, or reporting of human subjects research. At a minimum, include individuals who recruit or consent participants or who collect study data.

6. ADDITIONAL CONTACT ☐ N/A

If further information about this application is needed, specify the contact person if other than the PI (e.g., study or regulatory coordinator, research assistant, etc.).

Name (Last, First, MI):	**Ha, Richard, D**	Phone:	**614-634-1472**
E-mail:	**Ha.47@osu.edu**	Fax:	

7. EDUCATION

Have all OSU investigators and key personnel completed the required web-based course (CITI) in the protection of human research subjects?

- ☒ Yes
- ☐ No

Educational requirements (initial and continuing) must be satisfied prior to submitting the application for IRB review. See http://orrp.osu.edu/humansubjects/citi.cfm or contact ORRP for more information.

8. CONFLICT OF INTEREST

Does any **OSU investigator** (including principal or co-investigator), **key personnel**, or their immediate family members have a significant financial interest (e.g., speaking and consultation fees, travel expenses, proprietary interest in the tested product, stock ownership or other equity or membership in the sponsor over $10,000 per year or representing greater than 5% ownership in the sponsor) with the entity supporting the research or any company that may benefit from the research?

☐ Yes
☒ No

Each OSU investigator must have a current COI disclosure form filed before IRB review. See http://orc.osu.edu/coi/index.cfm for more information.

9. EXPEDITED REVIEW

Are you requesting **Expedited Review**?

☒ Yes → Complete **Appendix B**
☐ No

10. FUNDING

Is the research funded or has funding been requested? ☐ Yes ☒ No

If Yes → Specify sponsor _____ and provide OSU RF project number _____

If the research is federally funded and involves a subcontract to or from another entity, an IRB Authorization Agreement may be required. Contact ORRP for more information.

11. OTHER INSTITUTIONAL APPROVALS

Check all that apply and provide applicable documentation.

IRB review cannot be conducted* until other required approvals or exemptions are submitted.

☒ **None**

☐ **General Clinical Research Center Advisory Committee (GAC)** – for research conducted in the General Clinical Research Center (GCRC) or with any services provided by the GCRC. Contact 293-8750 or see www.gcrc.osu.edu.

☐ **Institutional Biosafety Committee (IBC)** – for research involving biohazards (recombinant DNA, infectious agents, select agents, toxins), gene transfer, or xenotransplantation. Contact 688-8457 or see http://orrp.osu.edu/biosafety.

☐ **James Cancer Center Clinical Scientific Review Committee (CSRC)** – for cancer-related research. Contact 293-4976 or see www.osuccc.osu.edu/csrc.

☐ **Maternal-Fetal Committee** – for research involving pregnant women and fetuses. Contact 293-8736.

☐ **Radiation Safety Committee** – for research involving radioactive material or use of ionizing radiation for research purposes (e.g., non-clinical care, including X-rays, PET scans, DEXA scans, and CT scans). Contact 292-1284 or see www.ehs.ohio-state.edu.

****IRB and GAC review may be performed concurrently; GAC approval must be provided to the IRB before you begin the research.***

12. LOCATION OF THE RESEARCH

a. List the specific site(s) at which the OSU research will be conducted (include both domestic and international locations).

Location Name (or description)	Street Address	City, State or Country
Room 443 Atwell Hall	**453 W. Tenth Ave**	**Columbus, OH**

b. Are all the sites named above on the OSU list of approved research performance sites? ***See http://orrp.osu.edu/humansubjects/researchsites.cfm or contact ORRP for more information.*** ☒ Yes ☐ No

If No → List the activities/procedures that will be performed at each location and who will be involved in each.

Location Name	Activity/Procedure Performed	Personnel (performing the activity/procedure)	Profession/Job Title	Organization

Research to be conducted at locations other than approved performance sites or involving non-OSU personnel may require a letter of support and/or another IRB's approval. Contact ORRP for more information.

13. SUMMARY OF THE RESEARCH

Summarize the proposed research using ***non-technical*** language that can be readily understood by someone outside the discipline. Explain briefly the research design, procedures to be used, risks and anticipated benefits, and the importance of the knowledge that may reasonably be expected to result. ***Use complete sentences (limit 300 words).***

This is a study of the acute effects of using an inspiratory threshold device (ITD). The study is to be single blinded, randomized, and quasi-experimental with repeated measurements. Subjects will be continuously observed and monitored using bioimpedance for non-invasive cardiac output and heart rate, respiratory frequency and pulse oximetry. Subjects will breathe through an ITD alternating between two-minute intervals of zero resistance and resistances of -7, -11, -15, and -19 cm H2O pressure. For randomization, subjects will select pre-set ITDs from a set of four. During each level of resistance, maximum changes from baseline of cardiac output, heart rate, blood pressure, breathing frequency and arterial oxygen saturation will be recorded and subjects will indicate their subjective feeling of exertion based on a Borg scale score from 1 to 10.

Breathing with inspiratory resistance may cause some subjects to experience some breathlessness like they are doing mild exercise. As a precaution, the study will be terminated for a subject if a subject reports a feeling of "very strong effort" (a Borg scale score of 6), if oxygen saturation falls to 90%, if blood pressure decreases or increases to 140/90, if heart rate decreases or increases to 85% maximum heart rate as determined by 0.85 (220-age).

Devices which are similar to ITDs are available as a means for inspiratory muscle training and to increase cardiac output in people while they are undergoing CPR. Correlating inspiratory threshold resistances with heart rate, cardiac output, and the Borg scale score to multiple pressures could give valuable insight on how the threshold pressures should be set during CPR. Results from this study may later be used to increase the efficacy of these devices.

14. SCIENTIFIC BACKGROUND & LITERATURE REVIEW

Summarize existing knowledge and previous work that support the expectation of obtaining useful results without undue risk to human subjects. ***Use complete sentences (limit 300 words).***

Previous studies of inspiratory threshold devices (ITD) use the term "cracking pressure" for the effort needed to allow inspiratory flow. Lurie (2003) reported decreased intrathoracic pressures in 6 anesthetized pigs breathing on an ITD at -10 cm H2O. Lurie (2004) studied cracking pressures to -20 cm H2O and reported that in less than 2 minutes at -12 cm H2O, systolic blood pressure and cardiac output increased significantly. Convertino (2004) measured heart rate, non-invasive blood pressure, stroke volume using bioimpedence while 20 healthy humans breathed on a ITD at -6 cm H2O. Compared to a sham, he found significantly higher stroke volume, heart rate, and cardiac output, significantly lower systolic blood pressure and no change in minute ventilation.

Cook (2007) studied the effect of a cracking pressure of -6 cm H2O on 8 healthy humans and found increases in mean arterial pressure and heart rate. Idris (2007) studied the effect of -7 cm H2O on 29 healthy humans and found no differences in heart rate, breathing frequency, or tidal volume, but the power of breathing increased significantly compared to a sham. Richards (2007) measured cerebral blood flow velocity in 8 adult human subjects experiencing progressive central hypovolemia exposed to lower body negative pressure who were breathing on an ITD of -7 cm H2O which delayed presyncopal symptoms.

Most studies have evaluated only one cracking pressure; none have included an assessment of imposed exertion while using the device, and there is no consensus as to what minimum cracking pressure should be used for its cardiovascular effects.

15. RESEARCH OBJECTIVES

List the specific scientific or scholarly aims of the research study.

The purposes of this study are to determine if relationships exist between cracking pressures of -7, -11, -15, and -19 cm H_2O and cardiac output, blood pressures, and Borg scale scores for healthy adults and to determine the maximum cracking pressure which does not produce a Borg score greater than 6.

The research questions are:

1) For the cracking pressures of -7, -11, -15, and -19 cm H_2O, are there statistically significant correlations between the magnitudes of cracking pressures and cardiac output, blood pressures, and Borg scale scores for healthy adults?

2) For the cracking pressures of -7, -11, -15, and -19 cm H_2O, what is the highest inspiratory threshold which produces exertion indicated as 6 on the Borg scale?

16. RESEARCH METHODS & PROCEDURES

a. Identify all procedures that are to be performed solely for the research study. Distinguish research activities from non-research activities.

We will apply 8 EKG-type monitoring leads and a finger probe to each subject. Subjects will be asked to breathe through plastic inspiratory threshold devices (ITD) for approximately 18-20 minutes. They will alternate between breathing through an ITD that gives zero resistance to inhalation and a randomly assigned pre-set ITD with a resistance of -7, -11, -15, or -19 cm H2O. They will breathe through the ITDs for two minute intervals in this sequence:

2 min	2 min	2 min	2 min	2 min	2 min	2 min	2 min	2 min
No Resistance	Randomly assigned resistance #1	No Resistance	Randomly assigned resistance #2	No Resistance	Randomly assigned resistance #3	No Resistance	Randomly assigned resistance #4	No Resistance

During the experiment, subjects will be continuously monitored non-invasively for cardiac output, pulse, breathing frequency, arterial oxygen saturation, and blood pressure. During each ITD interval, they will indicate their subjective feeling of exertion on a Borg scale from 1 to 10.

b. Check all research procedures that apply:

- ☐ Anesthesia (general or local) or sedation
- ☐ Audio, video, digital, or image recordings
- ☐ Biohazards (e.g., rDNA, infectious agents, select agents, toxins)
- ☐ Biological sampling (other than blood)
- ☐ Blood drawing
- ☐ Coordinating Center
- ☐ Data, not publicly available
- ☐ Data, publicly available
- ☐ Data repositories → Complete **Appendix C** (future unspecified use, including research databases)
- ☐ Deception → Complete **Appendix D** & **Appendix M1**
- ☒ Devices → Complete **Appendix E**
- ☐ Diet, exercise, or sleep modifications
- ☐ Drugs or biologics → Complete **Appendix F**
- ☐ Emergency research
- ☐ Materials that may be considered sensitive, offensive, threatening, or degrading
- ☒ Non-invasive medical procedures (e.g., EKG, Doppler)
- ☒ Observation of participants (including field notes)
- ☐ Oral history (does not include medical history)
- ☒ Placebo
- ☐ Pregnancy testing
- ☐ Program Protocol (Umbrella Protocol)
- ☐ Radioisotopes or other sources of ionizing radiation
- ☐ Radioactive materials (requires approval from Radiation Safety Committee)
- ☐ Randomization
- ☐ Record review (which may include PHI)
- ☐ Specimen research
- ☐ Stem cell research
- ☐ Storage of biological materials → Complete **Appendix H** (future unspecified use, including repositories)

- ☐ Focus groups
- ☐ Food supplements
- ☐ Gene transfer
- ☐ Genetic testing → Complete **Appendix G**
- ☐ Internet or e-mail data collection
- ☐ Magnetic Resonance Imaging (MRI)
- ☐ Surgical procedures (including biopsies)
- ☐ Surveys, questionnaires, or interviews (one-on-one)
- ☐ Surveys, questionnaires, or interviews (group)
- ☐ X-rays or microwaves
- ☐ Other

  Specify: _____

17. DURATION

Estimate the time required from each participant, including long-term follow-up, if any. Describe the time commitment in detail.

Each subject will participate in the study for less than 1 hour. We will devote approximately 10 minutes for explaining the procedures and obtaining informed consent, 10 minutes for application of EKG-type leads and set up of the equipment, 20 minutes for breathing with an ITD, and 10 minutes for removal of leads and any concluding discussion.

18. NUMBER OF PARTICIPANTS

a. Provide the maximum number of participants (or number of participant records, specimens, etc.) for whom you are seeking OSU IRB approval. **20 subjects**

The number of participants is defined as the number of individuals who agree to participate (i.e., those who provide consent or whose records are accessed, etc.) even if all do not complete the study.

b. Explain how this number was derived.

Similar studies evaluating similar variables determined there were significant differences in cardiac output using 10 healthy subjects. Based on the results of Convertino (2004), we determined that an "n" of 14 would have a power of 0.8. Another study by Convertino (2007) showed that an "n" of 7 would be insufficient to show any significant changes. Therefore, with the possibility of having subjects which do not complete the study, a total of 20 subjects are going to be recruited. We estimate the power of the study would increase to 0.9 if all 20 subjects complete for the study.

c. Is this a multi-center study? ☐ Yes → Indicate the total number of participants to be enrolled across all sites: _____
☒ No

The total number of research participants may be increased only with prior IRB approval.

19. PARTICIPANT POPULATION

a. Specify the age(s) of the individuals who may participate in the research:

Age(s): **> 18 years**

b. Specify the population(s) to be included (check all that apply):

- ☒ Adults
- ☐ Adults unable to consent for themselves
- ☐ Children (< 18 years) → Complete **Appendix I**
- ☒ Healthy volunteers
- ☐ Non-English speaking → Complete **Appendix J**
- ☐ Pregnant Women/Fetuses/Neonates → Complete **Appendix K**
- ☐ Prisoners → Complete **Appendix L**
- ☐ Psychology Research Education Program (REP)
- ☐ Student participant pool (other than REP)

  Specify: _____
- ☐ Unknown (e.g., research using secondary data/specimens, non-targeted surveys, program protocols)

c. Describe the characteristics of the population(s) and explain how the nature of the research requires/justifies inclusion of the proposed population(s).

The population is expected to be composed of healthy normotensive individuals who have no reported history of cardiopulmonary abnormalities. At the time of experimentation they are to have a blood pressure between 90/60 to 130/85, an arterial oxygen saturation

level of at least 95%, a negative inspiratory force of at least -60 mm Hg, a heart rate between 60 to 100 beats/min, a cardiac output between 3 to 6 Liters/min, and a respiratory rate between 12 to 20 breaths/min.

These types of individuals have to be evaluated in order achieve the purpose of the experiment which is to determine if relationships exist between cracking pressures of -7, -11, -15, and -19 cm H_2O and cardiac output and Borg scale scores for healthy adults and to determine the maximum cracking pressure which does not produce a Borg score of 6.

d. If pregnant women are to be excluded, explain how the nature of the research requires/justifies their exclusion. Address means of pregnancy screening.

Pregnancy may impact a subject's breathing pattern during mild exercise, similar to their breathing on an inspiratory threshold device. Previous studies done in other locations studying the effects of inspiratory threshold devices, such as the US army and NASA, have excluded pregnant women. Women will be asked during the telephone prescreening and after consent if they are pregnant. If they indicate that they are pregnant or may be pregnant during either one of those times, they will be excluded from the experiment.

20. PARTICIPANT IDENTIFICATION, RECRUITMENT, & SELECTION

a. Describe how potential participants will be identified (e.g., advertising, individuals known to investigator, record review, etc.). Explain how the method(s) for identifying potential participants respects their privacy.

Potential participants will be identified and recruited through advertising. Potential participants will not give their name unless they contact us to volunteer for participation in the study. All contact information and records of conversation will be destroyed if it is shown at any time that a potential participant is not eligible for the study or disinterested in participating in the study.

b. State who (investigators and/or key personnel) will recruit participants and what process will be used to determine participant eligibility.

A co-investigator will recruit subjects.

Potential participants will then contacted by phone to see if they qualify for the study and have the time to participate. While they are screened on the phone, they will be asked only general questions about their health. They will be asked about their cardiovascular and pulmonary health. They will not be asked about their psychological or personal histories. Only the researcher will have access to these people's contact information.

c. Describe the recruitment process, including how and where recruitment will take place. ***Provide copies of proposed recruitment materials (e.g., ads, flyers, website postings, recruitment letters, oral/written scripts).***

Potential participants will be recruited using fliers posted around The Ohio State University campus. People willing to participate will be asked to call or e-mail the contact information listed on the flier to indicate their interest. If the potential participant calls, they will be asked if they want to participate in the study and be screened then. If the potential participant sends an e-mail, the potential participant will be contacted by phone later on. They will be notified that they will be eligible for a raffle for gift certificates only after they passed the second screening.

Eventually, all potential participants will be screened initially by telephone. Potential participants then will be asked to schedule a second screening and participation in the experiment if they qualify for the study. They will also be sent a consent form and an information sheet explaining the study procedures. At the study site, they will decide whether to give consent to participate or not. If they give consent, potential participants will have their blood pressure, arterial oxygen saturation, negative inspiratory force, heart rate, cardiac output, and respiratory rate measured during their second screening. If they have a blood pressure between 90/60 to 130/85, an arterial oxygen saturation level of at least 95%, a negative inspiratory force of at least -60 mm Hg, a heart rate between 60 to 100 beats/min, a cardiac output between 3 to 6 Liters/min, and a respiratory rate between 12 to 20 breaths/min they will qualify for the study. If they qualify for the study, they will be eligible to for the raffle. They will also be considered "subjects" at this point. However, potential participants will be notified at both the phone screening and the second screening that they will be able to withdraw from the experiment at any time. They will still be eligible for the raffle if they give consent to participate and pass the first screening during the first telephone conversation and come in and pass the second screening.

d. Explain how you will assure that recruitment and selection of participants is equitable.

All subjects are pre-qualified on a "first-come-first-serve" basis.

21. INCENTIVES TO PARTICIPATE

Will participants receive compensation or other inducements (e.g., free services, cash payments, gift certificates, parking, classroom credit, travel reimbursement) to participate in the research study? ☒ Yes ☐ No

If Yes → Describe the inducement. ***Compensation should be pro-rated (e.g., per visit) and not contingent upon study completion.***

Potential study participants will eligible to win a raffle for gift certificates if they qualify for the study. Adequate results do not necessarily have to be acquired from them for them to be entered in the raffle. However, participants must qualify for the study after being screened by phone and being screened at the study site to be eligible for the raffle. They must demonstrate through the screenings that they are healthy normotensive individuals who have no reported history of cardiopulmonary abnormalities who, at the start of their study, have a blood pressure between 90/60 to 130/85, an arterial oxygen saturation level of at least 95%, a negative inspiratory force of at least -60 mm Hg, a heart rate between 60 to 100 beats/min, a cardiac output between 3 to 6 Liters/min, and a respiratory rate between 12 to 20 breaths/min.

22. INFORMED CONSENT PROCESS

a. Indicate the consent process(es) and document(s) to be used in the study. Check all that apply. Provide copies of documents (using OSU templates) and/or complete relevant appendices, as needed. ***See http://orrp.osu.edu/humansubjects/consent.cfm or contact ORRP for more information.***

- ☐ Assent – Form
- ☐ Assent – Verbal Script
- ☒ Informed Consent – Form
- ☐ Informed Consent – Verbal Script → Complete **Appendix M2**
- ☐ Informed Consent – Addendum
- ☐ Parental Permission – Form
- ☐ Parental Permission – Verbal Script → Complete **Appendix M2**
- ☐ Translated Consent/Assent – Form(s) → Complete **Appendix J**
- ☐ Waiver or Alteration of Consent Process → Complete **Appendix M1**
- ☐ Waiver of Consent Documentation → Complete **Appendix M2**

b. Describe the consent process. Explain when and where consent will be obtained and how participants and/or their legally authorized representatives will be provided sufficient opportunity to consider participation. ☐ N/A

Before potential participants arrive at the study site, they will be sent a consent form and an information sheet explaining the study. At the study site, potential participants will be given a verbal summary of the experiment. They will then be given documents to look at and sign. There will be a verbal explanation of the forms to the potential participants before they sign them. The second screening will not start unless they sign the forms.

c. List the investigator(s) and/or key personnel who will obtain consent from participants or their legally authorized representatives. ☐ N/A

Richard Ha will obtain consent from all potential participants.

d. Explain how the possibility of coercion or undue influence will be minimized in the consent process. ☐ N/A

Potential participants will volunteer their time and information.

e. Will any other tools (e.g., quizzes, visual aids, information sheets) be used during the consent process to assist participant comprehension? ☒ Yes → ***Provide copies of these tools.*** ☐ No

f. Will any other consent forms be used (e.g., for clinical procedures such as MRI, surgery, etc. and/or consent forms from other institutions)?
☐ Yes → ***Provide copies of these forms.***
☒ No

23. CAPACITY TO CONSENT

Will adult participants with limited decision-making capacity or who lack the ability to consent be recruited in this research study?
☐ Yes
☒ No

If Yes → Describe the likely range of participant impairment and explain how, and by whom, the capacity to consent/assent will be determined. For adults unable to provide legally effective informed consent, indicate whether assent will be obtained; or if not, explain why not.

24. PRIVACY & CONFIDENTIALITY

a. Does the research require access to personally identifiable private information?
☒ Yes
☐ No

If Yes → Describe the steps you will take to ensure protection of the participants' privacy.

Screening of the population for potential subjects will require the researchers to inquire information about the potential participant's current status of health and their contact information. During the phone screenings, if a potential participant is found to not qualify for the study, conversation with them will cease and all information acquired from them will be shredded and disposed of. All information from potential participants who qualify for the study will have their information stored on a password protected computer in 431 Atwell Hall. Potential participants will be assigned a numbered ID. Only investigators will have access to the information. The results from the study will be processed anonymously. All data that is acquired from them will be written on data acquisition sheets with only the potential participant's assigned number on them. Any written documentation that identifies the potential participant with their data will be shredded and disposed of once it is transferred to the password protected computer in 431 Atwell Hall. Only the investigators and co-investigators will have access to the contact and health information acquired from the potential participants.

b. Will personal or sensitive information (e.g., relating to illegal behaviors, alcohol or drug use, sexual attitudes, mental health, etc.) be accessed or collected from participants?
☐ Yes
☒ No

If Yes → Describe information.

c. Could disclosure of information be potentially damaging to participants' financial standing, employability or reputation, or place the participants at risk of criminal or civil liability?
☐ Yes
☒ No

If Yes → Explain.

d. Explain how you will protect the confidentiality of identifiable data, including where data will be stored, what security measures will be applied, and who will have access to the data.

Potential participants will be assigned a numbered ID. Only investigators will have access to the information. The results from the study will be processed anonymously. The data will only be stored on a password protected computer in 431 Atwell Hall.

e. Will you be obtaining a NIH Certificate of Confidentiality? ***See http://grants2.nih.gov/grants/policy/coc/index.htm***
☐ Yes → ***Provide a copy before you begin the research.***
☒ No

f. Explain any circumstances (ethical or legal) where it would be necessary to break confidentiality.
☒ N/A

g. Indicate what will happen to the identifiable data at the end of the study. Check all that apply:

- ☒ Identifiers separated or permanently removed from the data
- ☐ Identifiable/coded data is retained
- ☐ Other, specify: _____
- ☐ N/A

h. Indicate how study results might be disseminated. Check all that apply:

- ☒ Conference/Presentation
- ☒ Dissertation/Thesis
- ☒ Publication/Journal article
- ☐ Other, specify: _____

25. HIPAA RESEARCH AUTHORIZATION

Will individually identifiable Protected Health Information (PHI) subject to the HIPAA Privacy Rule requirements be accessed, used, or disclosed in the research study?

- ☐ Yes
- ☒ No → Go to Question #26

If Yes → Will a written authorization be used?

☐ **Yes →** ***Provide a copy of the Authorization Form.***

a. Describe the PHI involved in the research (e.g., demographic information, health history, diagnosis, test results). Be as specific as possible. ***Provide a copy of the data collection form(s) to be used.***

b. List the source(s) of the PHI (e.g., OSUMC Information Warehouse, physician's own records, etc.), including whether any information will be obtained from sources external to OSU.

☐ **No →** Indicate the type of waiver or alteration requested (check all that apply) and complete **Appendix N.**

- ☐ Partial Waiver (recruitment purposes only)
- ☐ Full Waiver (entire research study)
- ☐ Alteration (written documentation)

26. RISKS, HARMS, & DISCOMFORTS

a. Indicate all risks/harms/discomforts that may apply to the research study:

- ☐ Breach of confidentiality
- ☐ Discovery of previously unknown condition
- ☐ Economic risk
- ☐ Invasion of privacy (participants or other individuals)
- ☒ Physical injury or discomfort
- ☐ Psychological stress
- ☐ Risk to reputation
- ☐ Social or legal risk
- ☐ Other
  Specify: _____

b. For each category of risk checked above, describe the specific risk. For physical injury or discomfort include the following:

- Frequency/likelihood of occurrence
- Potential severity of the harm/discomfort
- Possible consequences (including long-term effects)

Reference the section of this application (e.g., Appendix F for drugs) if the risks are described elsewhere.

The subjects may exert enough effort breathing through the device to feel like they are doing mild exercise. They may feel symptoms similar to mild exercise such as shortness of breath or fatigue. However, the likelihood of these symptoms becoming severe will be minimal since the participants are to be healthy individuals; whereas, the devices they going to breathe on are designed for people with chronic obstructive pulmonary disease. There are no consequences or long term effects from participating in the study.

c. Describe the specific protections that will be used to minimize the identified risks and harms.

Subjects will be continuously observed, and the subject's arterial oxygen saturation and cardiac function will be continuously monitored using a pulse oximeter, noninvasive cardiac output monitor and blood pressure. As a precaution, the study will be terminated for a subject if a subject reports a feeling of "very strong effort" (a Borg scale score of 6), if oxygen saturation falls to 90%, if blood pressure decreases or increases to 140/90, if heart rate decreases or increases to 85% maximum heart rate as determined by 0.85 (220-age).

27. MONITORING

Does the research involve greater than minimal risk (i.e., are the harms or discomforts described in Question #26 beyond what is ordinarily encountered in daily life or during the performance of routine physical or psychological tests)? ☐ Yes ☒ No

If Yes → Describe the plan to oversee and monitor data collected to ensure participant safety and data integrity. Include the following:

- The information that will be evaluated (e.g., incidence and severity of actual harm compared to that expected);
- Who will perform the monitoring (e.g., investigator, sponsor, or independent monitoring committee);
- Timing of monitoring (e.g., at specific points in time, after a specific number of participants have been enrolled); and
- Decisions to be made as a result of the monitoring process (e.g., provisions to stop the study early for unanticipated problems).

28. REASONABLY ANTICIPATED BENEFITS

List the potential benefits that participants, society, and/or others may expect as a result of this research study. State if there are no direct benefits to individual participants. ***Compensation is not to be considered a benefit.***

Devices using a similar principle are being marketed in the United States and Europe as a way to increase cardiac output to a patient undergoing CPR. Although, research has shown the devices to be effective at increasing cardiac output, there has not been a clear standard as to how various inspiratory resistances affects cardiac output or a person's perception to breathing effort. The results from the study would give insight as to how people feel and what their cardiac output is at different inspiratory resistances. A clear standard inspiratory resistance setting may then be identified after evaluating the results of this study increasing the efficiency of the devices.

There is no direct benefit to the individual participants who volunteer for the study.

29. ASSESSMENT OF RISKS & BENEFITS

Discuss how risks to participants are reasonable when compared to the anticipated benefits to participants (if any) and the importance of the knowledge that may reasonably be expected to result.

There is a possibility that the participants may experience mild discomfort or fatigue while participating in the experiment. However, usage of the device requires minimal effort. Breathing through the device is like breathing through a straw. While there are no direct benefits to the participants, the data acquired from evaluating their physiological variables on different cracking pressures will help determine optimal settings of impedance threshold devices used in resuscitation.

30. ALTERNATIVES TO STUDY PARTICIPATION

Other than choosing not to participate, list any specific alternative procedures or treatments available that may be advantageous to the participant.

There are no alternative procedures or treatments.

31. PARTICIPANT COSTS/REIMBURSEMENTS

a. List any potential costs participants (or their insurers) will incur as a result of study participation (e.g., parking, study drugs, diagnostic tests, etc.).

Parking.

b. List any costs to participants that will be covered by the research study.

None.

32. APPLICATION CONTENTS

Indicate what documents are being submitted for this research project. Check all appropriate boxes and provide the version number and date, if available.

		Version	Date
☒	**Initial Review of Human Subjects Research Application**	1.3	6/11/2007
☒	Appendix A1: Co-Investigators (question 4)	1.3	6/11/2007
☐	Appendix A2: Key Personnel (question 5)		
☒	Appendix B: Expedited Review – Initial Review (question 9)	1.3	6/11/2007
☐	Appendix C: Data Repositories (question 16b)		
☐	Appendix D: Deception (question 16b)		
☒	Appendix E: Devices (question 16b)	1.3	6/11/2007
☐	Appendix F: Drugs or Biologics (question 16b)		
☐	Appendix G: Genetic Testing (question 16b)		
☐	Appendix H: Storage of Biological Materials (question 16b)		
☐	Appendix I: Children (question 19b)		
☐	Appendix J: Non-English Speaking Participants (question 19b and 22a)		
☐	Appendix K: Pregnant Women/Fetuses/Neonates (question 19b)		
☐	Appendix L: Prisoners (question 19b)		
☐	Appendix M1: Waiver or Alteration of Consent Process (questions 16b & 22a)		
☐	Appendix M2: Waiver of Consent Documentation (question 22a)		
☐	Appendix N: Waiver of HIPAA Research Authorization (question 25)		
☒	**Research Protocol (required)**		
☐	Grant Application (required for all sponsored projects not part of a cooperative group)		
☐	DHHS-approved Protocol (required for DHHS-supported multicenter clinical trials)		
☐	DHHS-approved Consent Form (required for DHHS-supported multicenter clinical trials)		
☒	Assent Form(s), Informed Consent Form(s), Informed Consent Addendum, Parental Permission Form(s), Translated Consent/Assent Form(s), Verbal Script(s) (question 22a)		12/14/2007
☐	Supplemental Consent Form(s), Consent Tool(s) (question 22e and 22f)		
☐	HIPAA Research Authorization Form (question 25)		
☒	Recruitment Materials (e.g., ads, flyers, TV/radio scripts, internet solicitations) (question 20c)		12/14/2007
☒	Script(s) or Information Sheet(s), including Debriefing Materials (question 16b)		12/14/2007
☐	Instruments (e.g., questionnaires or surveys to be completed by participants) (question 16b)		
☐	Data Collection Form(s) involving PHI (question 25)		
☒	Device Manufacturer's Approved Labeling (Appendix E)	1.3	6/11/2007
☐	Drug Manufacturer's Approved Labeling/Investigator's Drug Brochure (Appendix F)		
☐	Other Committee Approvals/Letters of Support (questions 11 & 12)		
☐	Other		

Specify: _____

33. ASSURANCE

PRINCIPAL INVESTIGATOR (or Advisor)

I agree to follow all applicable policies and procedures of The Ohio State University and federal, state, and local laws and guidance regarding the protection of human subjects in research, as well as with professional practice standards and generally accepted good research practice guidelines for investigators, including, but not limited to, the following:

- The research will be performed as approved by the IRB under the direction of the Principal Investigator (or Advisor) by appropriately trained and qualified personnel with adequate resources;
- The research will not be initiated until written notification of IRB approval has been received;
- Informed consent and HIPAA research authorization from human subjects (or their legally authorized representatives) will be obtained and documented (unless waived) prior to their involvement in the research using the currently IRB-approved consent form(s) and process;
- Serious, unexpected and related adverse events, unanticipated adverse device effects, and unanticipated problems involving risks to participants or others will be promptly reported to the IRB, as well as any other information necessary for appropriate oversight of the research;
- Significant new findings that develop during the course of the study that may affect the risks or benefits of participation will be reported;
- The IRB will be informed of any proposed changes in the research or informed consent process before changes are implemented, and no changes will be made until approved by the OSU IRB (except where necessary to eliminate apparent immediate hazards to participants);
- A Continuing Review of Human Subjects Research application will be completed and submitted before the deadline for review at intervals determined by the IRB to be appropriate to the degree of risk (but not less than once per year) to avoid expiration of IRB approval and cessation of all research activities;
- Research-related records (and source documents) will be maintained in a manner that documents the validity of the research and integrity of the data collected, while protecting the confidentiality of the data and privacy of participants;
- Research-related records will be retained and available for audit for a period of at least three years after the research has ended (or longer, according to sponsor or publication requirements) even if I leave the University;
- The Office of Responsible Research Practices will be contacted for assistance in amending (to request a change in Principal Investigator) or terminating the research if I leave the University or am unavailable to conduct or supervise the research personally (e.g., sabbatical or extended leave);
- A Final Study Report will be provided to the IRB when all research activities have ended (including data analysis with individually identifiable or coded private information); and
- All Co-Investigators, research staff, employees, and students assisting in the conduct of the research will be informed of their obligations in meeting the above commitments.

I verify that the information provided in this Initial Review of Human Subjects Research application is accurate and complete.

Signature of Principal Investigator (or Advisor) _____ Date _____

Printed name of Principal Investigator (or Advisor) _____

DEPARTMENT CHAIR (or Signatory Official)

As Department Chair (or Signatory Official) for the Principal Investigator, I acknowledge that this research is in keeping with the standards set by our unit and that it has met all Departmental/College requirements for review.

If the PI or any Co-Investigator is also the Department Chair, the signature of the Dean or other appropriate Signatory Official, such as the Associate Dean for Research, must be obtained.

Signature of Department Chair _____ Date _____

Printed name of Department Chair _____

APPENDIX B
Expedited Review – Initial Review

Complete this form to request expedited review of the proposed research. If the research meets the conditions for expedited review, the review of the protocol will be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

See 45 CFR 46 and 21 CFR 56 for more information.

PI Name: F. Herbert Douce

Conditions required for expedited IRB review:

1) The Federal Regulations establish two main criteria for an expedited review:
   a) The research may not involve more than "minimal risk". "Minimal risk" means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (45 CFR 46.102(i) and 21 CFR 56.102(i)).
   b) The entire research project must be consistent with one or more of the federally defined categories.
2) The categories in this list apply regardless of the age of the participants, except as noted. The expedited review procedure may not be used where identification of the participants and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participant's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
3) The expedited review procedure may not be used for classified research involving human subjects or research involving prisoners as participants.
4) Investigators and IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review (i.e., expedited or convened) utilized by the IRB.

Select the category that best describes the research project.

☐	(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.) (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
☐	(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week. (b) from other adults and children (defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a)), considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

☐	(3) Prospective collection of biological specimens for research purposes by non-invasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
☒	(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
☐	(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)
☐	(6) Collection of data from voice, video, digital or image recordings made for research purposes.
☐	(7) Research made on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Appendix C

Mass Recruitment E-mail

PLEASE SEND ALL REPLIES TO ha.47@osu.edu

Hello Fellow SAMP Student,

My name is Richard Ha. I am a Medical Technology student who is seeking volunteers for a research study being done at Atwell Hall. I am hoping you can lend me an hour of your time during the month of July to participate in my study.

The study would require you to breathe through a plastic mouthpiece device for 20 minutes and wear some EKG pads while I monitor your cardiac function. I attached a flier which describes the requirements of the participants in some detail. There will be a drawing for two $25.00 VISA debit cards for those who participate in the study. I am hoping to recruit 20 people.

Will you please participate in my study? To schedule your hour, please see available times posted at http://amp.osu.edu/rt/research-schedule.cfm and SEND AN E-MAIL TO ha.47@osu.edu with 1 or 2 selected dates/times. I'll reply to confirm and send you the consent form.

If you have any questions, I can be reached at ha.47@osu.edu or 614-634-1472.

Thanks,

Richard D. Ha

RESEARCH STUDY IN NEED OF VOLUNTEERS

Are you a >18, healthy, non-smoker, not pregnant person who can walk for 20 minutes?

If yes, you can help us test a breathing device with potential use in CPR.

- **No blood samples or biopsies**
- **Study is one hour**
- **All participants are eligible to win a $25.00 VISA debit card.**

If interested, please contact:

Richard Ha

Honors Student, Allied Medical Professions

e-mail: ha.47@osu.edu

phone: 614-634-1472

Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu	Breathing Study Call 614-634-1472 Email ha.47@osu.edu

Telephone script

Caller: Hi, I [saw your flier or got word] about a research study you are conducting and would like to volunteer for it.

Researcher: Well, thanks for calling. Yes, I am the one recruiting people to participate in our research project. The name is Richard. May I ask what your name is?

Caller: [Caller gives name]

Researcher: Nice to hear from you [caller]. Well, talking about the project, there are a few things I need to check. First, are you at least 18 years old?

Caller: [Caller answers "yes" or "no." If caller says "yes," conversation will continue. If caller says "no," researcher will attempt to end the conversation and politely indicate to the caller that they will not qualify for the experiment.]

Researcher: "Yes?" Well good. Have you ever had any health problems with your heart or lungs?

Caller: [Caller answers "yes" or "no." If caller says "no," conversation will continue. If caller says "yes," researcher will attempt to end the conversation and politely indicate to the caller that they will not qualify for the experiment.]

Researcher: "No?" Glad to hear you are well. Do you smoke?

Caller: [Caller answers "yes" or "no." If caller says "no," conversation will continue. If caller says "yes," researcher will attempt to end the conversation and politely indicate to the caller that they will not qualify for the experiment.]

Researcher: "No" is good. Are you pregnant or do you suspect that you may be pregnant?

Caller: [Caller answers "yes" or "no." If caller says "no," conversation will continue. If caller says "yes," researcher will attempt to end the conversation and politely indicate to the caller that they will not qualify for the experiment.]

Researcher: Okay. Have you had any trouble walking for twenty minutes?

Caller: [Caller answers “yes” or “no.” If caller says “no,” conversation will continue. If caller says “yes,” researcher will attempt to end the conversation and politely indicate to the caller that they will not qualify for the experiment.]

Researcher: Well, you passed our initial phone screening. I will tell you a little bit about the study now. Please feel free to ask me questions at any point. You ready for a big explanation?

Caller: [Caller answers “yes” or “no.” If caller says “yes,” conversation will continue. If caller says “no,” researcher will attempt to end the conversation or break the one upcoming explanation into smaller explanations if the caller requests it.]

Researcher: We are conducting a research project called, “The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion. The study takes a look at how your heart would respond and how you would feel while breathing on a spring loaded device called an “Inspiratory Muscle Trainer.” During the study, we would require you to breathe through that plastic device. It is kind of like breathing through a straw and it offers adjustable resistances to your breathing. We would also ask that you allow us to place some pads on your chest and neck to let us monitor your heart. All the tools being used are safe and being sold to hospitals right now. The whole procedure would last for about an hour.

We are conducting this study in room 443 Atwell hall. You would have to go through another health screening set up for you at the study site that would check your blood pressure, heart rate, respiratory rate, how much oxygen is in your blood, strength of your lungs, and cardiac output to see if your measurements are normal. As a result, you would have to wear loose fitting clothing. If you pass our screenings, qualify for our study, and consider participating in our study, you will be eligible to win a raffle we are holding for all subjects. After hearing all that, would you be willing to participate in our study?

Caller: [Caller answers “yes” or “no” and asks specific questions if necessary. If subject says “yes,” conversation will continue. If caller says “no,” researcher will attempt to end the conversation and politely thank the caller.]

Researcher: Great! When are you available to come see us?

Caller: [indicates availability]

Researcher: Thanks very much. We will see you then. Do you have any more questions?

Caller: [Caller answers “yes” or “no.” If caller says “yes,” conversation will continue. If caller says “no,” researcher will attempt to end the conversation and politely thank the caller.]

Confirmatory E-mail

Thanks for volunteering.

Before we get started, I have a few questions to ask. Please e-mail me your replies.

Are you at least 18 years old?

Have you ever had any health problems with your heart or lungs?

Do you smoke?

Are you pregnant or do you suspect that you may be pregnant?

Have you had any trouble walking for twenty minutes?

Please let me know if you have anymore questions. I attached more information concerning the study on this e-mail. They include a consent form and an information sheet about the study. Please refer to #3 on the consent form if you would like to know what exactly will be done.

I hope to hear from you soon.

When you come in for the experiment, it is highly recommended you wear a t-shirt and a sport's bra or something to cover you up. We are going to ask you to place the EKG leads on yourself in a secluded place, then wear your t-shirt over the leads.

I will also send you a reminder e-mail a couple of days before you are supposed to come in.

Appendix D

The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion

For this study we would do the following things:

1. We would attach the following devices on you.
    - A device to measure the oxygen in your blood that clips on to the outside of your finger.
    - Heart Monitor
    - Blood Pressure Cuff

2. You would breathe through several of these.

Inspiratory Muscle Trainers

3. You would be switching devices every two minutes. We will hand you the one you need to be breathing on. You will do this nine times.

4. We would ask you to evaluate how "Out of Breath" you feel every two minutes. You will point to a number on a chart to indicate this. The chart will look like this.

0	No effort
0.5	Very, very slight effort (just noticeable)
1	Very slight effort
2	Slight effort
3	Moderate effort
4	Somewhat strong effort
5	Strong effort
6	Very strong effort
7	
8	
9	Very, very strong effort (almost maximal effort)
10	Maximal effort

The Modified Borg Scale for Perceived Exertion

Appendix E

The Ohio State University Consent to Participate in Research

Study Title: **The Evaluation of Multiple Impedance Thresholds on Cardiac Output and Perceived Exertion**

Principal Investigator: **F. Herbert Douce**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

We want to see how your heart responds and how you feel while breathing on a plastic device called an "Inspiratory Muscle Trainer" at different settings.

2. How many people will take part in this study?

Twenty people are expected to participate in this study.

3. What will happen if I take part in this study?

We will have you wear clips on your nose, a blood pressure cuff on your arm, some pads from a heart monitor on your chest, and an oxygen sensor clip on your finger. These instruments will monitor your heart, blood pressure, pulse, breathing rate, and how much oxygen is in your blood, before starting the study. If any of your measurements are abnormal, you cannot participate in this study and we will recommend you see a medical professional. If all of your measurements are normal, we will then ask you to breathe on an "Inspiratory Muscle Trainer" we give to you. This Inspiratory Muscle trainer will feel like you are breathing through a big straw. It will be very easy to take a breath through this device. We will then ask you to randomly pick one of four Inspiratory Muscle Trainers we have in a box and ask you to breathe on that device for two minutes. This device will feel like you are breathing through a smaller straw. After two minutes, you will set aside the device and go back to breathing on the Inspiratory Muscle Trainer that feels like you are breathing through a big straw. You will not place that Inspiratory Muscle Trainer back in the box. After another two minutes, we will ask you to repeat the process and pick another Inspiratory Muscle Trainer from the box. During this whole time, we will monitor your heart, blood pressure, pulse, breathing rate, and how much oxygen is in your blood. There will be five different Inspiratory Muscle Trainers that you will breathe on. They will be set at five different settings. Breathing on each of these Inspiratory Muscle Trainers will be like breathing through five different size straws. With each Inspiratory Muscle Trainer, we will ask how you feel, on a scale from 0 to 10, while breathing on it.

4. How long will I be in the study?

After getting your permission, we will need one hour of your time to screen and run the test on you. 20 minutes will be needed to screen you and 40 minutes will be needed to run the test.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.

6. What risks, side effects or discomforts can I expect from being in the study?

You may feel that you are doing some exercise while participating in our study. The study requires you to suck in air through a "straw-like" device that will make it slightly more

difficult for you to take in air. You may have to spend some extra energy trying to suck in air through this plastic device. As a result, you might experience some fatigue or feel "out of breath" while trying to take in some breaths with this device in your mouth. However, you will recover quickly when you stop breathing through the device.

We will also place some pads on your skin that are attached to a heart monitor. There is a risk of slight skin irritation from using the pads of the heart monitor.

When monitoring your heart and oxygen from the sensor clip, we may discover some health abnormalities. You may get upset by this.

At any point we discover health abnormalities or find your health at risk, you will be requested to stop our experiment and advised to consult with a health professional.

7. What benefits can I expect from being in the study?

You will not receive any benefits for participating in our study.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

The personal information we will acquire from you will be kept confidential. We will not use your name when evaluating your study-related information. The data we collect from you will be filed under a study subject number. The list matching your name with a number will be put on a password protected computer and destroyed at the end of the raffle. If you choose not to participate in our study, we will destroy all information that we acquired from you.

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law. Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and

- Your insurance company (if charges are billed to insurance).

If the study involves the use of your protected health information, you may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form.

10. What are the costs of taking part in this study?

There are none, unless you have to pay for parking.

11. Will I be paid for taking part in this study?

You will not receive any compensation for participation in this study. However, you will be eligible to enter in our raffle for two $20.00 gift certificates if you pass our screening and qualify for participation in our study. The possibility of getting one of these gift certificates is 1 in 10. You will be notified by e-mail if you are randomly selected to receive a certificate.

By law, payments to subjects are considered taxable income. If you are an OSU employee, any compensation you receive as a result of participating in the study will be made through the payroll system and applicable taxes will be deducted.

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact **Mr. F. Herbert Douce at 614-292-8445**.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Mr. F. Herbert Douce at 614-292-8445**.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**AM/PM** **Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time

Appendix E

Richard Ha (Member ID: 101423)

CITI Collaborative Institutional Training Initiative

Resources | Main Menu | Select Language | Logoff

Modules Completed

Module	Date Last Completed	Exam ID
101 Refresher Course - An Overview of Research with Vulnerable Subjects (ID: 985)	01/19/08	15033643
101 Refresher Course - FDA Regulated Research and Conference on Harmonization (ID: 987)	01/19/08	15033832
101 Refresher Course - History and Ethics (ID: 975)	01/19/08	15033178
101 Refresher Course - Pregnant Women and Fetuses (ID: 986)	01/19/08	15033769
101 Refresher Course - Records Based Research (ID: 983)	01/19/08	N/A
101 Refresher Course - Social and Behavioral Research (ID: 982)	01/19/08	15033506
101 Refresher Course - Complete the course (ID: 990)	01/19/08	N/A
101 Refresher Course - Informed Consent (ID: 980)	01/19/08	15033447
101 Refresher Course - Regulations and Process (ID: 981)	01/19/08	15033312
101 Refresher Course - Research with Vulnerable Populations - Minors (ID: 974)	01/19/08	15033689
Basic Institutional Review Board (IRB) Regulations and Review Process (ID: 2)	01/13/05	2104038
Conflicts of Interest in Research Involving Human Subjects. (ID: 681)	01/19/08	15034024
FDA-Regulated Research (ID: 12)	01/18/05	2128323
Genetic Research in Human Populations (ID: 6)	01/14/05	2111373
Group Harms: Research With Culturally or Medically Vulnerable Groups (ID: 11)	01/17/05	2121546
HIPAA and Human Subjects Research (ID: 14)	01/19/05	2128386
HIPAA and Human Subjects Research. (ID: 526)	01/19/08	15033937
History and Ethical Principles (ID: 498)	01/13/05	2100015
Human Subjects Research at the VA (ID: 13)	01/19/05	N/A
Informed Consent (ID: 3)	01/13/05	2106237
Introduction (ID: 757)	01/12/05	N/A
Ohio State University (ID: 780)	01/19/08	N/A

Records-Based Research(ID: 5)	01/14/05	2111324
Refresher Course 101 Introduction(ID: 960)	01/17/08	N/A
Research With Protected Populations - Vulnerable Subjects: An Overview(ID: 7)	01/14/05	2111391
Social and Behavioral Research for Biomedical Researchers (ID: 4)	01/14/05	2111272
Students in Research - SBR(ID: 1321)	01/29/08	N/A
Vulnerable Subjects - Research Involving Minors(ID: 9)	01/17/05	2121341
Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero(ID: 10)	01/17/05	2121464
Vulnerable Subjects - Research with Prisoners(ID: 8)	01/17/05	2117767

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